IntechOpen

Endoscopy

Innovative Uses and Emerging Technologies

Edited by Somchai Amornyotin

ENDOSCOPY - INNOVATIVE USES AND EMERGING TECHNOLOGIES

Edited by **Somchai Amornyotin**

Endoscopy - Innovative Uses and Emerging Technologies
http://dx.doi.org/10.5772/59220
Edited by Somchai Amornyotin

Contributors

Kenro Kawada, Pierre Cordelier, Louis Buscail, John Calleary, Bret Burgess, Puru Naidu, Ratislav Hejj, Thomas A. Lee, Arjuna De Silva, Boonsam Roongpuvapaht, Kangsadarn Tanjararak, Ake Hansasuta, Matteo Cavaliere, Maurizio Iemma, Kris Jatana, Kris R. Jatana, Patrick Walz, Charles Elmaraghy, Taku Sakamoto, Yutaka Saito, Alfredo J. A. Barbosa, Anca Oana Docea, Paul Mitrut, Adina Kamal, Liliana Streba, Nicolae-Dragos Margaritescu, Sorin Ioan Zaharie, Costin Teodor Teodor Streba, Joachim Oertel, Guilherme Ramina Montibeller, Lela Migirov, Michael Wolf, Giulia Cossu, Mahmoud Messerer, Roy Daniel, Mercy George, Fabrice Parker, Nozar Aghakhani, Marc Levivier, Abdulzahra Hussain, George Pados, Anastasios Makedos, Borislav Vladimirov, Somchai Amornyotin

Notice

First published in Croatia, 2015 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

Additional hard and PDF copies can be obtained from orders@intechopen.com

Endoscopy - Innovative Uses and Emerging Technologies
Edited by Somchai Amornyotin

p. cm.

ISBN 978-953-51-2172-5

eBook (PDF) ISBN 978-953-51-7258-1

Meet the editor

Dr. Somchai Amornyotin graduated at the Faculty of Medicine Siriraj Hospital, Mahidol University in 1989. He became a member of staff of the Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand in 1996. By 2004 he became the associate professor of the Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University. From 2005 until 2009 he was the head of Anesthesiology Division of Siriraj GI Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University. His first scientific paper was published in Thailand in 1999. He has practiced anesthesia for gastrointestinal endoscopy since 2002. He was a member of the committee of Siriraj GI Endoscopy Center, Faculty of Medicine Siriraj Hospital in 2005. More than 50 of his articles have been published in Thai and international medical journals. Dr. Amornyotin is a member of the Royal College of Anesthesiologists of Thailand, the Gastroenterological Association of Thailand and many scientific societies. He is the reviewer and editor of many international journals.

Contents

Preface

Endoscopy is a fast moving field, and new techniques are continuously emerging. In recent decades, endoscopy has evolved and branched out from a diagnostic modality to enhanced video and computer assisting imaging with impressive interventional capabilities. The modern endoscopy has seen advances not only in types of endoscopes available, but also in types of interventions amenable to the endoscopic approach. To date, there are a lot more developments that are being trialed. In fact, there are multiple researchers and physicians attempting to innovate the field of endoscopy.

Minimal invasive procedure aims to minimize trauma of the interventional process but still achieves a satisfactory therapeutic result. It is commonly performed because of several advantages such as reduced post-procedural pain, faster recovery and more rapid return to normal activities, shorter hospital stay, and reduced post-procedural complications. Modern endoscopic equipment provides physicians with the benefit of many technical advances. Endoscopy is an effective and safe procedure even in special populations including pediatric patients and renal transplant patients. It serves as the tool for diagnosis and therapeutic interventions of many organs including gastrointestinal tract, head and neck, urinary tract and others. In this book, the authors will discuss some of the emerging techniques, innovations and technologies used to increase the diagnostic and therapeutic yield in various organs.

The contributions in this book are very valuable. InTech Open Access Publisher selected several known names from many countries with different levels of development. Multiple specific points of view were presented together with several topics regarding diagnostic or therapeutic endoscopy. The readers can take into consideration the practical knowledge in the endoscopic field. This book actually represents a valuable tool for formation and continuous medical education in the endoscopy considering the performances or technical possibilities in different parts of the world.

I very much appreciate and thank all the authors of this book. Many thanks to InTech Open Access Publisher which offered me the possibility of editing this attractive book. It was a real pleasure to read such interesting works by so many experts from all over the world. Finally, I also thank Ms. Iva Lipović for her perfect, prompt and efficient co-operation.

Assoc. Prof. Somchai Amornyotin MD, FRCAT
Department of Anesthesiology and Siriraj GI Endoscopy Center
Faculty of Medicine Siriraj Hospital
Mahidol University, Bangkok, Thailand

Section 1

General Aspects

Chapter 1

Guidelines for Reprocessing Non-Lumened, Heat-Sensitive ENT Endoscopes

Matteo Cavaliere and Maurizio Iemma

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61219

Abstract

Endoscopes have become an indispensable instrument in the ENT department, but their use has introduced potential health risks such as the infection transmission.

Numerous guidelines have been issued for both digestive and respiratory endoscopes, while to date specific references to ENT endoscopes do not exist. The diagnostic ENT endoscope does not generally have an operative channel, it is shorter, thinner and has a much more frequent usage. As a consequence the guidelines for digestive or respiratory endoscopes are not always functional for the ENT department.

This paper proposes:1. to standardize the correct way to carry out the disinfection procedure of heat-sensitive non-lumened ENT endoscopes, 2. to guarantee the disinfection within a limited time frame, appropriate for an ENT out-patients department.

In the initial phase the critical areas encountered in ENT endoscopy were determined. This was followed by a research of the literature in order to identify existing guidelines for the reprocessing of endoscopes with a view to establishing a common disinfection procedure of non-lumened ENT endoscopes. Finally, the new methods of disinfection, developed specifically for the reprocessing of ENT endoscopes were examined and discussed.

Keywords: Heat-sensitive ENT endoscopes, Cleaning, Disinfection

1. Introduction

The introduction of the endoscopes into clinical practice has certainly improved the diagnosis and treatment of numerous pathologies, but has also brought the risk of transmission of infections.

In the Literature, [1] the incidence of infection appears to be 1 per every 1,800,000 endoscopic procedures performed (0.000056%).

Considering the high number of endoscopic procedures performed daily worldwide, the endoscopy-related infections are those most often associated with the medical device.

In nearly all of the infections transmitted, the problem is a defect in the cleaning and disinfection procedures, [2, 3, 4] in particular during

- the pre-washing step (12%),
- the washing/disinfection step (73%),
- drying and storage (12%).

Flexible endoscopes are heat-sensitive and therefore cannot be sterilised in an autoclave, but must be disinfected. [5]

In otorhinolaryngology, unlike digestive and respiratory endoscopy, to date, no specific guidelines yet exist. ENT diagnostic endoscopes do not have the operating channel, their size is smaller and their use is more frequent, including in outpatient situations.

Then, the guidelines used in digestive and respiratory endoscopy are not always functional in the ENT department, since they do not consider the dynamism and intensity of the work carried out there.

2. Objectives

This document proposes to

1. standardise the correct method of disinfection procedures for heat-sensitive, non-channelled ENT endoscopes,
2. reduce the risk of transmitting infections,
3. increase operator safety,
4. guarantee disinfection in fast times.

3. Methods

In the initial phase, we identified the main critical procedures within ENT endoscopy departments. Next, we researched the literature to find all the guidelines on reprocessing endoscopes.

http://dx.doi.org/10.5772/61219

Lastly, we discussed the new disinfection methods designed specifically for the reprocessing of ENT endoscopes.

In order to form a basis for the guidelines for the reprocessing of flexible ENT endoscopes, the working group decided to conduct a survey among the Italian ENT departments with the objective to gather information regarding the methodologies actually employed for the disinfection of heat-sensitive, non-lumened endoscopes. Two hundred and seventy two questionnaires were sent out to the ENT departments. The questionnaire was divided into six sections: the first dealt with general information, sections 2 to 5 considered the four principle reprocessing methods of flexible ENT endoscopes (automated, manual immersion, wipes and sheaths). The last section considered the storage of the endoscopes.

The information requested referred to the way the endoscope was reprocessed by each participant and an evaluation of the method in relation to the needs of the department.

4. Survey findings

The following general considerations emerged from the study:

- The average number of endoscopic visits per day was around 10 and the majority of the doctors referred to difficulties in performing more examinations due to the limited number of instruments and the time necessary for reprocessing.
- Reference to guidelines is made in just above 30% of cases, they are not always the same and generally refer to gastroendoscopes/bronchoscopes (Figure 1).

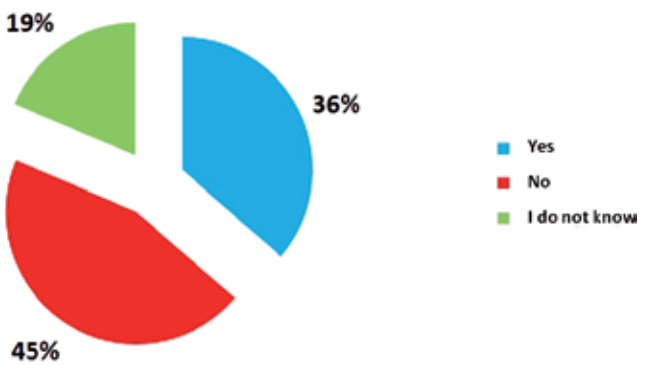

Figure 1. Dear Authors, Please add caption

- *Manual immersion is the principle method (about 70% of cases)* for the disinfection of ENT endoscopes (Figure 2), followed by the sheath, which in 50% of cases is used in conjunction with other methods. The automated endoscope reprocessor (AER) is present in about 20% of the departments, but in over 60% of cases is used in conjunction with other systems, evidence maybe of the difficulties of habitual usage.

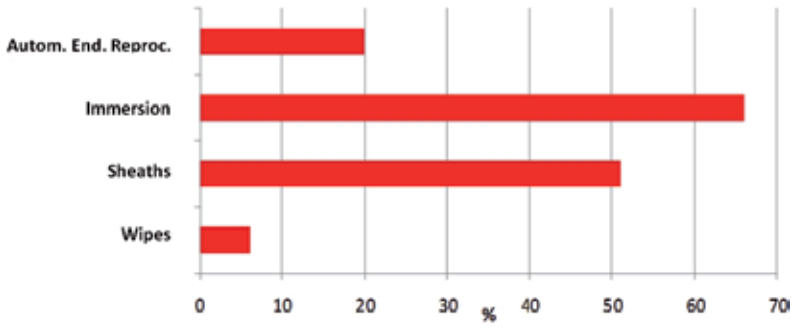

Figure 2. Dear Authors, Please add caption

a. Immersion

- Immersion is the most utilized method, both as a sole method and as a method used in conjunction with others. A basin or tray is mostly utilized for the immersion of the instrument.
- The leak test is performed in about 80% of cases.
- The enzymatic detergent is mostly used in the pre-cleaning step (about 50% of cases), while simple soap and water in about 20%. The time taken for pre-cleaning is normally less than 5 minutes, but can exceed 15.
- At least in 42% of cases the same detergent is re-used. It must be remembered that the detergent does not have any biocidal activity and so it is plausible that microbes can survive in the solution. As a consequence, a new solution should be used on each occasion.
- A wide variety of disinfectants are used for the disinfection step, mainly peracetic acid based, but also glutaraldehyde and orthophthalaldehyde are used (Figure 3).

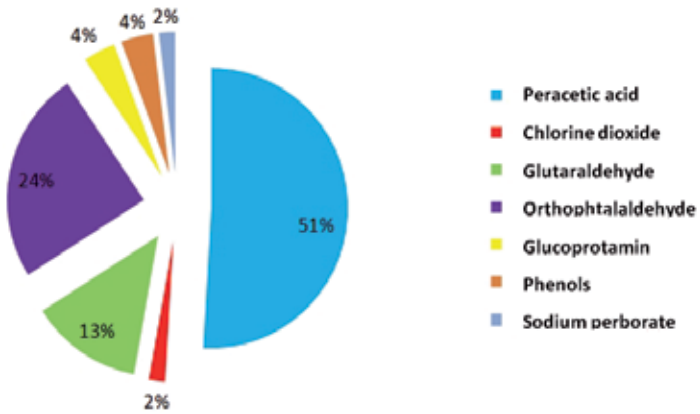

Figure 3. Dear Authors, Please add caption

http://dx.doi.org/10.5772/61219

- From an analysis of the disinfectants used, it was noted that not all the products have been tested according to current European norms (EN 14885) and that different contact times have been indicated for the same product. *It is therefore important to underline that even if the disinfectants have the same molecular base, the formulations may be different and consequently the way in which they are used can be different.*
- The majority of disinfectants are multi-use which makes it difficult to implement a traceability system.
- For 75% of cases, the rinse step is performed by using tap water and is completed in less than 5 minutes.
- *The use of a traceability system is practically impossible with a re-usable disinfectant, but 95% of the respondents would appreciate a registration system.*
- In the evaluation of the method employed, *the respondents highlighted the problems of traceability and personal protective equipment.*
- The sheath is used in more than 30% of cases after disinfection, mainly for patients with a perceived risk of infection.
- Microbiological controls of the instrument are performed in less than 20% of cases.

b. Sheaths

- About 30% of ENT departments use exclusively the sheath. *It is mainly used in conjunction with other reprocessing methods, primarily for cases where the instrument must be used on patients with a recognized risk of infection.*
- Respondents expressed a critical evaluation regarding:
  1. the less than optimal adherence of the sheath,
  2. possible damage to the instrument, particularly during removal (50% of respondents),
  3. possible tearing of the sheath (17% of cases),
  4. reduced image quality (70% of respondents),
  5. patient discomfort, particularly children.
- The main reason for using the sheath is for better instrument turnaround (Figure 4), which can mean less expenditure for instruments. Avoiding cross-contamination and chemical products and practical usage are other important motivations.
- The overall evaluation is positive, but some *perplexity remains, particularly regarding traceability and the cost/benefit relationship* (from the sample the average cost of the sheath is around €10, but it can cost up to €25).
- The literature regarding the use of the sheath is limited, but where it exists, it is clearly indicated that the instrument needs to be cleaned and disinfected with ethanol after the sheath is removed in order to be equivalent with high-level disinfection. From the replies this occurs in only 2% of cases.

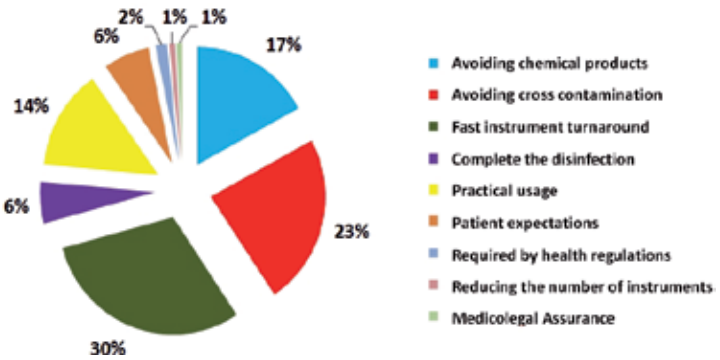

Figure 4. Dear Authors, Please add caption

- Microbiological controls are performed in 17% of cases and leak tests in 82%.

c. Automated endoscope reprocessors (AERs)

- In most cases, they are used in conjunction with sheaths (more than 50% of cases).
- In more than 33% of cases, the AER is not located in the department but in a central sterilization centre, affecting instrument rotation times.
- Cycle times vary between 20 and 30 minutes, which when added to the time for transporting endoscopes (when the endoscope is reprocessed outside the department) means that *the rotation time is about 1 hour in 70% of cases.*
- Pre-cleaning is mainly performed with an enzymatic detergent (75% of cases), but soap and water or only water are also used.
- The automatic reprocessors use mainly chemical disinfectants, notably single-use peracetic acid.
- The AERs can contain up to four instruments per cycle and in 75% of cases, both flexible and rigid scopes at the same time.
- Rinsing is normally performed while the instrument is automatically dried in only 50% of cases.
- The majority of AERs provide a confirmation print out for validation purposes, but the print outs are not always filed in a special record book.
- Microbiological controls are performed in 50% of cases, normally on a monthly basis and leak tests are nearly always performed.

d. Wipes

- They are used by less than 10% of respondents probably due to their recent introduction.
- The leak test is performed less often compared to other systems (60% of cases).

- The overall evaluation is favourable, both regarding the practicality and the traceability.
- For patients with a known risk of infection, normally the sheath is also used.

e. Storage

There are diversified methods of storing the instrument between one visit and another (Figure 5).

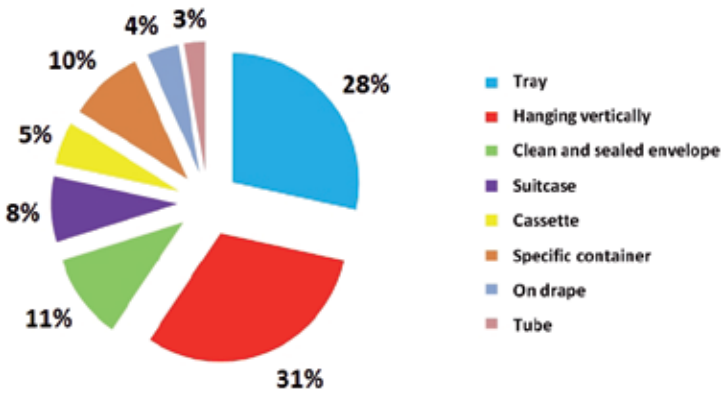

Figure 5. Dear Authors, Please add caption

It is worth noting that about 10% of respondents store the instrument in its case, which actually represents one of the main sources of contamination.

From the answers, it can be seen that over 50% of respondents believe the instrument can be contaminated during storage, but, despite this risk, the disinfection cycle is performed in only 33% of cases on instruments being taken out of storage.

5. Principle problems related to endoscope reprocessing

Schematically, the problems most frequently encountered with endoscope reprocessing are associated with [6]:

- environment,
- organization of endoscopic activity,
- personnel.

Problems associated with the environment:

1. the room or the disinfection area is not equipped with an extractor hood despite the use of certain disinfectants where it is specified,
2. the presence of a sharp smell due to the disinfectant solution,

3. insufficient space in relation to the volume of activity,
4. no distinct separation between dirty and clean work surfaces,
5. environmental cleaning can be of poor quality.

Problems associated with the organization of endoscopic activity:

1. excessive volumes of activity in relation to staff allocation and equipments available.
2. unplanned endoscopic examinations affect the organization of the programmed work.

Problems associated to personnel:

1. Insufficient number of nurses,
2. the personnel are not aware of the reprocessing procedures or, when they are available, they are not known or shared,
3. respect of safety precautions by the operators is not optimal,
4. specific training of the personnel involved is not always performed.

6. Principles of hygiene in the endoscopic procedures [7, 8]

Abiding to the basic principles of hygiene represents the foundation for the control of risks of infection associated with endoscopic procedures.

These basic principles must be applied to

- equipment and medical devices,
- environmental surfaces,
- health operator behaviour.

The equipment and medical devices*are the principle vehicles for cross-infections in that they are continually contaminated by microbes originating from assistance to patients.*

They must be carefully cleaned and subjected to a process of high-level disinfection (or sterilization in the case of devices which can be placed in the autoclave) according to the indications of the manufacturer.

The environmental surfaces*are likewise a vehicle* for cross-infections in that they are continuously contaminated not only by environmental microbes but also by those originating from assistance to patients. The objective of the cleaning and disinfection of the surfaces is to ensure a low-level bacterial count and interrupt the risk of transmission of pathogens. *Sanitization should be performed with water and detergent*.

Disinfection should be performed preferably with chlorine-based disinfectants to ensure the destruction of the more resistant microbes.

http://dx.doi.org/10.5772/61219

The area where the disinfection of the endoscope takes place should be distinct from where the endoscopic examination is performed. A separate and specific room is "highly preferable"; but in the reality of the ENT department, unlike others such as gastroenterology, it is possible that the reprocessing of the endoscope is carried out in the same room as the patient's examination. It is necessary therefore *to highlight the need to ensure a clear division between contaminated areas (where the used instruments are placed) and clean areas (from where the reprocessed instruments are picked up)* so that the used instruments are completely separate from the reprocessed ones, avoiding risks of cross-contamination.

The *wash basins* should be of adequate dimension to allow the complete immersion of the instruments, without causing damage, preferably in steel (ceramic basins can be the cause of damage due to knocks to the terminal part of the instrument).

The necessity or not to install an extractor hood should be evaluated in function of the room and the equipment installed. It is absolutely necessary and essential if chemical products are used in open containers. Automatic systems which incorporate a device for the handling of vapours do not necessarily require the hood.

Where the room is not naturally ventilated, an *air ventilation system* needs to be installed (supply and extraction) in order to reduce to a minimum the exposition of everybody to the potentially harmful vapours (e.g. glutaraldehyde). In Italy, the limit of 10 air changes per hour is considered acceptable.

Operator behaviour*is critical for the prevention of cross-infections. Fundamentally, the principle that all patients are potential carriers of infections should be considered.*

Standard precautions

- should be applied by all health operators for all patients who receive assistance, irrespective of the diagnosis or the presumed state of infection,
- have the objective protecting health personnel and patients,
- should be based on the following healthcare practices:
  1. washing of hands and use of gloves,
  2. use of face masks, eye protection, smocks.

Written procedures should be present in all working environments with clear indications of each stage of the process.

Personnel must be taught to apply the "standard precautions" published periodically by the C.D.C. (Control Diseases Center of Atlanta) for infection control and should know:

- the procedure for cleaning and disinfecting each device,
- the conduct to follow in case of an alarm or malfunctioning of equipment,
- the biological and chemical risks which can be incurred during the disinfection procedure and how they should be encountered.

The responsibility of the disinfection procedure for endoscopes is attributed both to the nursing staff and to the doctor using the instrument. [5]:

- *the nurse and healthcare operator* are responsible for performing decontamination, pre-cleaning and disinfection of the equipment,
- *the head nurse of the operating unit* is responsible for verifying that the procedure is carried out correctly,
- *the doctor* using the instrument must visibly check that the instrument has been reprocessed before performing the examination,
- *the head consultant of the operating unit* is responsible for overseeing organizational aspects.

Endoscopes are very delicate instruments and therefore should be handled only by trained operators authorized to use and disinfect them.

The ENT operating unit together with the infection control unit should organize courses to train how to use and disinfect the endoscopes correctly and should keep an up to date list of all authorized personnel.

7. Risk of infection in endoscopy

The sources of infection are represented by infected or colonized patients [9] and by environment [10], in particular, the water used to rinse the endoscopes. Where possible, rinsing in sterile water is recommended. Differently, rinsing in high-quality drinking water is also acceptable using a bacteria-retentive filtering system (0.2 μ).

An observational study [11] conducted at 26 hospitals in the United States revealed that the endoscopes and bronchoscopes can be improperly disinfected due to inappropriate disinfectant solution, lack of control of the disinfectant's concentration, failure to clean all the parts of the endoscope and failure to measure manual disinfection times.

The *degree of risk* is classified as

- low when there is contact with healthy skin,
- intermediate when there is contact with the mucous membranes or superficially damaged skin,
- high for penetration into tissue or sterile cavities or into the vascular system.

The degree of risk determines the reprocessing level of the instrument used: *the risk of infection of the ENT endoscopes* (entering into contact with mucous membranes or damaged skin) *is intermediate and the high-level disinfection is then required.* [12, 7, 8]

High-level disinfection presumes the inactivation of all the bacteria, mycobacteria, fungi and viruses, but not necessarily of all bacterial spores. In ENT this is sufficient to have a guarantee regarding the transmission of pathogenic microorganisms for both the doctor and the patient.

http://dx.doi.org/10.5772/61219

7.1. High-level disinfection of endoscopes: traditional and emerging methods [13– 14]

We have categorized disinfection systems into two types:

1. *Traditional:*
   - *Immersion:* the operator manually performs all the steps of the disinfection,
   - *Automatic:* the disinfection is handled automatically without manual intervention,
2. *Emerging,* methods designed specifically for the ENT department:
3. *Complete reprocessing using wipes,*
4. *Immersion systems electronically controlled by a microprocessor:* part of the process is handled by the operator and part occurs automatically,
5. *Sterile protective sheaths*: constitute a protective barrier of the endoscope and not a system of disinfection.

The steps to reprocess endoscopes common to all traditional disinfection systems are described in Table 1. We must first emphasize the following points:

1. *reprocess the endoscope immediately after use* to prevent the formation of encrustations and consequent damage to the instrument.
2. *the entire endoscope must be cleaned and disinfected:* to be avoided are the wall tubes fitted in cui only the insertion tube of the instrument is placed, preventing contact between the control head and the disinfectant.

After analysing the reference literature, the authors suggest the following recommendations divided according to the type of disinfection system (Table 2).

In the following, we provide in detail the main considerations and evaluations for each system presented.

8. Traditional systems

1. Manual disinfection system by immersion

The manual procedure is relatively inexpensive but has the following disadvantages:

- errors or forgetfulness,
- lack of traceability,
- risk of contact between operators and contaminated material,
- damage to the instruments,
- disinfection times of at least 20 minutes.

2. Automatic disinfection systems

While until very recently only automatic systems for gastroscopies and bronchoscopies were available, today several companies realized washer-endoscopes for non-channelled ENT endoscopes.

The automatic systems can

- automatically cleanse, disinfect and dry,
- perform only the disinfection step.

These systems are composed of

- a tub for the disinfectant and one for the cleaning solution,
- a basin with a cover for the positioning of the endoscope. Washer-disinfector-endoscopes normally can reprocess several endoscopes simultaneously,
- a panel for setting the washing cycle (in general, the time and the temperature of the washing and disinfection sequences).

The disinfectant is transferred from the tub to the basin containing the endoscope and remains here for the time indicated on the technical sheet. This is followed by rinsing and the endoscope is ready for re-use.

In order to reduce the risk of contaminations, the washer-disinfector-endoscopes are usually equipped with thermal auto-disinfection systems.

It is advisable to position washer-disinfector in well-ventilated areas separated from those in which occurs the endoscopic examination.

When buying a washer-disinfector-endoscope, one should pay attention to the following aspects:

- automatic loading of cleanser and disinfectant,
- capacity to reprocess more than one endoscope simultaneously,
- programmability,
- the possibility of performing a complete cycle of cleansing, disinfection and rinsing,
- cycle time,
- the type of disinfectants for which the system is certified and their cost per cycle,
- the possibility of performing auto-disinfection/auto-sterilization,
- the presence of visual and sound alarms,
- required space,
- registration of procedures performed, an aspect strongly advised today because of medical–legal lawsuits. In general, the data that is recorded and/or printed are
    - identification number of the instrument;

http://dx.doi.org/10.5772/61219

- details of the operator;
- operating parameters relating to procedures;

- date and time of the procedure.

The automatic procedures therefore

- standardizes the process, reducing the possibility of errors,
- allows the immersion of the entire endoscope,
- makes it possible to "track" the procedures by printing a receipt after every disinfection cycle,
- reduces the risk of contact between operators or environment and contaminated instruments,
- reduces the risk of damage to endoscopes.

The main disadvantages are

- the cost of equipment and maintenance expenses; *some companies have product-specific washer-disinfector-endoscopes for ENT, smaller and less expensive* (Figure 6),

Figure 6. Dear Authors, Please add caption

- the possibility of recontamination of the endoscopes by the same washer-disinfector,
- time required for the disinfection process (in general at least 20 minutes).

9. Emerging systems

9.1. Manual disinfection system with wipes

The disinfection system by means of wipes is a manual sporicidal disinfection treatment of semi-critical, non-channelled and heat-sensitive endoscopes.

The active ingredient used is chlorine dioxide (ClO_2), patented under the name "Tristel".

The Tristel Wipe System consists of a wipe for the pre-disinfection cleaning step, a wipe for the disinfection process and one for the post-disinfection rinsing step. The mechanical wiping action increases the efficacy of the cleaning and disinfection. The wipes are single-use and thus permit tracking of the procedures.

Treatment time is only 2–3 minutes allowing a notable reduction in disinfection times compared with other disinfectants in immersion methods. The Tristel Wipe System was in fact designed for the rapid turnaround of the ENT endoscope.

In addition, the wipes are non-toxic and non-irritating, thus allowing manual wiping technique not possible with the other traditional high-level disinfectants.

This simple system, however, is manual and can lead to different results between the various operators: accurate training is necessary to ensure that all operators are capable of optimal performance.

9.2. Immersion disinfection system electronically controlled by a micro-processor

This is a high-level disinfection system of the endoscopes by immersion controlled electronically. *The time necessary for disinfection is 5 minutes*, but the overall treatment time depends on the cleaning and rinsing method used, respectively, before and at the end of disinfection.

The system (Figure 7) consists of a base unit with a cover in which the instrument is placed, after cleaning, and to which is added the high-level disinfectant, ClO_2-based [15, 16].

Figure 7. Dear Authors, Please add caption

http://dx.doi.org/10.5772/61219

At the end of the disinfection cycle, the disinfectant is automatically emptied out in the sink and the instrument is rinsed manually.

At the end of the treatment, the base unit can be used as an aseptic container for short-term storage and/or for transport of the endoscope. The base unit and the cover are made of polycarbonate resin and can tolerate up to 30 autoclave cycles.

The micro-processor records every disinfection cycle and the recorded data can be downloaded on to the PC and archived, making it possible *to track the entire process*.

Placing the instrument in the empty unit and removing it only when the disinfectant is emptied out *avoids any skin contact with the disinfectant.*

Furthermore, the system is easily transportable because no connection to the electrical network is necessary; the only installation requirement is its positioning close to a sink in order to empty out the used disinfectant.

The immersion system with electronic control, by means of the micro-processor, ensures adequate contact time with the disinfectant and potentially damaging chemical overexposure, in addition to the ability to track the entire procedure.

9.3. Sterile protective sheaths

This is an endoscope encasing system that can represent an alternative to the high-level disinfection of endoscopes (Figure 8).

Figure 8. Dear Authors, Please add caption

Various studies [17, 18] have demonstrated *the necessity to clean the entire endoscope with an enzymatic cleanser, followed by a disinfectant with 70% ethanol*, immediately after the removal of the sheath, in order to guarantee the equivalent of a high-level disinfection. In fact, it was seen that small viruses are capable of penetrating the sheath.

From our investigation conducted at ENT departments in Italy in 2010, we have seen that the practice of cleaning and disinfecting is done in only 2% of cases after removal of the encasing.

The advantage of this system is *the speed*.

The *disadvantages* are represented by:

- an increase of the diameter of the endoscope with the subsequent discomfort for the patient,
- the possibility of contamination of the control head unprotected,
- the risk of breakage of the sheath during the exam [19],
- the possibility of damage to the endoscope when removing the sheath,
- vision is not optimal,
- costs: endoscopes of various brands moreover require specific sheaths and their cost ranges from 8 to 25 euros.

To remember:

- The choice of disinfection systems should be made in agreement between the head of the operating unit, the hospital pharmacy, the hospital infection control committee and the indications of the endoscope manufacturer.
- Endoscopes which cannot be fully immersed should be substituted.
- Instruments should be reprocessed immediately after use because if allowed to dry for a long period, the residues can become encrusted and even damage the instrument.
- If the endoscope is immersed for too long a period, the outer casing and the seals can be damaged.
- The endoscopic examination should be avoided for patients with suspected Creutzfeldt-Jakob disease (prions are resistant to all forms of conventional sterilization). When the endoscope is considered really necessary, a dedicated endoscope should be used, maybe single-use, or else an instrument which is reaching the end of its life cycle. After use, the endoscope must be put in quarantine until definitive confirmation of the pathology.

10. Disinfection of endoscopes contaminated by HVB, HVC, HIV or mycobacterium [20, 21]

At the time of writing, there have been no reports of the transmission of viruses by means of bronchoscopes, while cases of the transmission of HBV and HBC by means of gastroendoscopes inadequately reprocessed have been reported.

The majority of viruses, including HVB, HVC and HIV, are quickly neutralized with disinfection solutions. The major risks of virus transmission reside in the unsuccessful removal of

http://dx.doi.org/10.5772/61219

biological residues during the manual pre-clean, which allows the virus to avoid contact with the disinfectant.

Mycobacterium are responsible for an elevated percentage of contamination incidents referred to in the literature. All cases of tuberculosis have been attributed to the failed observance of infection control procedures.

Although some authors have sustained the need for longer disinfection times for endoscopes after use in patients affected by mycobacterium, this strategy is not required if infection control guidelines are carefully followed. Numerous studies have, for example, demonstrated that immersion for 20 minutes in a basic 2% solution of glutaraldehyde at 20°C, after an adequate pre-clean, significantly reduces the bacterial count of *M. Tuberculosis*.

11. Disinfection of endoscopes contaminated by prions [22– 23]

Prions are responsible for transmissible spongiform encephalopathy (TSE), capable of provoking degenerative diseases to the central nervous system in animals and man.

The most frequent disease from prions is Creutzfeldt Jakob Disease (CJD); other forms include variant Creutzfeldt Jakob Disease (vCJD), Gertsmann Straussler Scheinker syndrome (GSS), Fatal Familial (FFI), insomnia and Kuru.

Prions are resistant to common disinfectant substances. The tissues at high risk of infection include the brain, the dura mater, the spinal cord and the eyes, while tissues at low risk include cerebrospinal fluid, liver, lymph nodes, kidneys, lungs and spleen.

There have been no indications of cases of CJD attributable to devices contaminated with blood. Recognized cases of CJD as iatrogenic have been attributed to contaminated medical devices such as cerebral electrodes, cerebral neurosurgical instruments, dura mater grafts, corneal grafts, gonadotropins and human growth hormones.

From an analysis of the literature, it can be deduced that *endoscopes (apart from those used in neurosurgery) are devices which do not normally come into contact with tissues at risk of TSE* and consequently, even when used during diagnostic procedures on high-risk patients, standard reprocessing protocols are adequate.

The primary and principle preventive measure, however, in the case of high-risk patients, is *to limit endoscopic examinations exclusively to when necessary. If the examination is effectively necessary, it is advisable to designate one endoscope for such patients also for the future.*

In the case of an endoscopic examination which envisages contact with high and low risk tissues in a probably or certainly infected patient, the WHO guidelines indicate special treatments (sodium hydroxide, sodium hypochlorite, phenol, sterilization in autoclave) which are not compatible with endoscopes.

Seeing that the most common disinfectants used for endoscopes are not efficacious and considering the high cost of the instrument, some authors suggest covering the endoscope with a plastic sheath as a partial protection which can be eliminated after use as a special waste.

The ENT endoscopic procedures can, however, be managed without any special precautions due to the fact that the tissues with which there is contact are not considered infectious. For these patients, the standard protocols of pre-cleaning and high-level disinfection are adequate.

12. Biological controls

The monitoring infections resulting from endoscopic procedures cannot be an indicator of the efficacy of disinfection since infections are rarely linked to the execution of the endoscopic exam performed.

Moreover, the culture methods currently in use have not been rigorously validated, with the danger of underestimating or overestimating results, consequently causing potential harm to patients and health facilities. [24]

In the absence of adequate scientific evidence, the APIC (Association for Professionals in Infection Control and Epidemiology) and the CDC (Centres for Disease Control and Prevention) do not recommend routine microbiological tests and advise them *only in cases of epidemics*.

13. Tracking systems [5]

In every endoscopy unit, it is desirable to have a registration system in which the following information would need to be recorded for each procedure:

- examination number,
- patient generality,
- doctors and nurses generality,
- type of procedures,
- time,
- endoscope identification number,
- type of disinfection carried out.

The nursing coordinator of the unit should maintain

- documentation relating to installation, testing and maintenance of the washer-disinfector-endoscope machines (up to 5 years following the end of service),
- user's manuals for all the equipment,

http://dx.doi.org/10.5772/61219

- registration of biological controls carried out on the washer-disinfector-endoscope machines and on the endoscopes (at least 5 years),
- a copy of the print-out issued by the washer-disinfector-endoscopes, certifying the disinfection cycle (at least 5 years).

14. Disinfectants for the reprocessing of heat-sensitive, non-lumened ENT endoscopes

The survey findings indicated that peracetic acid and orthophthalaldehyde are the high-level disinfectants most commonly used for endoscopes. Chlorine dioxide is a disinfectant which is being increasingly used over the past few years.

Often, it is possible to find different disinfection solutions used for the same type of endoscope in the same hospital, and the use of a disinfectant as opposed to another is dependent on the operating unit.

Before examining the principle disinfectants, it is necessary to consider the following points regarding choice and usage [25, 26]:

1. Disinfectants must be registered at the Health Ministry and the technical bulletin should clearly indicate

- how to use,
- concentrations,
- contact times,
- temperature,
- pH.

2. Choose the disinfectant which is compatible with the endoscope in accordance with the indications of the instrument manufacturer.

3. The choice of solutions should be made in agreement with the pharmacy, health management and the heads of the operating units involved.

4. The disinfectants in use must be managed and stored in such a way as to avoid contamination (for example, containers handled with dirty hands and gloves, partial closure of packaging, etc).

5. When the disinfectant is re-usable, it is necessary

- to test the minimum effective concentration (MEC) at the beginning of the day. Results should be documented and the solution discarded when inferior to MEC,

- discard the disinfection solution at the end of the indicated usage period irrespective of the MEC. In cases where the disinfectant is added to AERs, the determination of the expiry date should be based on the original preparation date.

Monographs of the most commonly used disinfectant solutions are reported below *according to the information supplied by the manufacturers and the data from scientific literature.*

14.1. Glutaraldehyde (e.g. Cidex, Asep, Glutaster basica, Sporex) [27, 28]

Active ingredient

Glutaraldehyde or glutaric aldehyde in aqueous solution has a colourless or verging on yellow clear appearance and a pungent odour. The most common usage is a *2% alkaline* solution.

Characteristics

Glutarladehyde is mainly commercialized in an acid form which is stabile for long periods when stored in cool conditions and in tightly closed container (up to 5 years).

Before use, glutaraldehyde must be "activated" by adding a buffer and surfactant in order to obtain a pH of 7.5–8.5. The activator (e.g. bicarbonate) is supplied separately and is used to obtain a working solution *stable for 14 days.* This period of validity refers to the activated solution in its original bottle, while the period of reusability should be considered in function of the concentration level, generally not less than 1.5% (the concentration diminishes in time and in function of the number of disinfections).

Mode of action

Glutaraldehyde is also defined as glutaric dialdehyde because it is endowed with two aldehydic groups (CHO), positioned at the extremes of the molecule, which are the real source of biocidal action; they are directly involved in the alkylation of sulphide, carboxylic, amino and hydroxyl groups of the proteins of the microorganism, causing an irreversible alteration of the protein synthesis and the nucleic acids.

Glutaraldehyde is not deactivated significantly by organic material even though its presence renders the disinfection less effective due to the fixative capability of glutaraldehyde, which creates a protective covering that prevents the destruction of the microbial cells. It is recognized in fact that glutaraldehyde is not efficacious against biofilm.

Spectrum of activity

The spectrum of activity of glutaraldehyde is almost complete but the contact times vary notably according to conditions, e.g. a 2% solution in laboratory has been demonstrated to be active in

- 1–2 minutes against bacteria in vegetative form (e.g. *Staphylococcus aureus*, including the penicillin, *Pseudomonas aeruginosa*, *Escherichia coli*),
- 5–10 minutes against viruses (e.g. *Poliovirus* Type 1, *Coxsackie* B1, ECHO 6, *Rotavirus*, HAV, HBV, HCV, HTLV-III/LAV),

http://dx.doi.org/10.5772/61219

- 10 minutes against yeasts, fungi and moulds (e.g. *Trichophyton interdigitalis*, *Microsporum gypseum*, *Candida albicans*, *Aspergillus niger*),
- 20 minutes against *Mycobacterium tuberculosis* whereas the activity is slower against other types of mycobacterium (at least 60 minutes) due to the lipidic component in the cellular wall which makes them almost impermeable. The contact time can be reduced by using a 3–4% solution and/or increasing the temperature to 25°C,
- 3 hours against spores. Concentrations less than 2% do not offer guarantees of being sporicidal, even with an increase in the contact time.

Material compatibility

Glutaraldehyde is not corrosive to metals and does not present particular problems for rubber, plastic, glass and optical fibres. It is necessary, however, to take precautions:

- objects in carbon steel should not remain in contact with the solution for more than 24 hours.
- it is necessary to avoid contact between different metals during immersion (danger of causing an electrolytic reaction, capable of corroding instruments).

Toxicity/precautions

Glutaraldehyde is a toxic, irritant and sensitizing substance and can cause, in the case of inadequate rinsing, rhinoconjunctivitis, asthma, diarrhoea and abdominal cramp.

The main risk of glutaraldehyde toxicity is run by the staff who have to handle it, because:

- frequent contact with the skin can cause dermatitis and a persistent yellow or brown colouring of the skin,
- contact with the eyes can cause reddening of the conjunctiva or grievous damage to the cornea.
- irritation to the conjunctiva with burning, lachrymation and reddening,
- damage to the respiratory system with bronchitis, dyspnoea, bronchial asthma,
- damage to the central nervous system with headache, depression,
- ingestion can cause from moderate to marked irritation to the mouth, throat, oesophagus and stomach, pains in the chest and abdomen, nausea, vomiting, diarrhoea, dizziness, drowsiness, shock.

The product did not result to be carcinogenic, for inhalation, on laboratory animals after continued exposure.

The literature reports TLV/TVA[1]values from 0.2 to 0.05 ppm.

For these reasons *the use of glutaraldehyde must*

1 Threshold limit value-time weighted average: average concentration of a chemical agent weighted on an exposure level of 8 hours and for 40 hours per week, to which operators may be exposed without adverse effects for their health being apparent.

1. *Envisage the use of adequate personal protective equipment:*
    - protective eyewear,
    - authorized ventilators with filters for organic vapours, only in the presence of elevated vapours,
    - protective smock,
    - butyl or nitrile gloves or a double pair of latex gloves.
2. *Envisage use in a ventilated environment, in closed containers and in the presence of adequate extraction systems.*
3. Envisage staff training for correct usage and relative information regarding toxicity.

In the case of exposure, the first aid measures depend on the affected site:

- Contact with eyes: wash with plenty of water for at least 10 minutes. Remove contact lenses if possible to do easily. Visit the optician.
- Skin contact: remove contaminated clothes and wash with soap and water the affected parts of the skin. Consult a doctor if irritation persists.
- Ingestion: the product can cause ulceration and inflammation of the upper digestive system; it is preferable, therefore, not to cause vomiting but to resort to a cautious gastric lavage.
- Inhalation: transfer the person to a ventilated area. Artificial respiration may be necessary.

The use of glutaraldehyde as a high-level disinfectant is in constant decline, not particularly for reasons of efficacy, but rather for reasons linked to staff health and safety issues. It is worth noting that this chemical solution can no longer be used in British hospitals.

Disposal

The starting concentration of glutaraldehyde (2%) is possibly harmful. The concentration level, however, diminishes progressively due to re-use, evaporation and progressive dilutions.

According to Italian legislation, which has adopted European norms, disposal of the exhausted solution to sink is permitted, considering the high levels of dilution by water used daily for patient care. The sink must, however, be in a well-ventilated environment and disposal should be followed by running water to accelerate the discharge. Attention must be taken disposing large quantities directly into the sewers due to possible damage to the purification system through the inhibition of bacterial activity.

Indications for use

2% glutaraldehyde is indicated for the high-level disinfection of endoscopes and semi-critical medical devices with a contact time of not less than 20 minutes at a temperature of 20°C or more.

A contact time of 1 hour is advisable for bronchoscopes due to the slower mycobacterial activity. A satisfactory sporicidal activity is achieved after 3 hours.

http://dx.doi.org/10.5772/61219

After studying glutaraldehyde residues in plastic and rubber, after immersion in 2% glutaraldehyde, it was concluded that a 2 minute rinse is sufficient to significantly reduce the quantity of the active ingredient absorbed in the exposed material, with the exception of natural rubbers for which a prolonged soak and rinse is recommended.

14.2. Orthophthalaldehyde (e.g. Cidex OPA, Opaster) [29– 30]

Active ingredient

An aromatic dialdehyde in commerce for a few years also in Italy, generally used at a concentration of 0.55% in an aqueous solution, with a lowly accentuated odour and blue colour. It is stable at 15–30°C for 2 years.

Characteristics

Unlike glutaraldehyde, orthophthalaldehyde (OPA) is ready to use and does not require activation. Once opened, the unused solution can be stored in the original bottle for up to 2 months while the solution poured into the disinfection tray can be used for no more than 14 days, providing that the concentration level is superior to the MEC (at least 0.3%) indicated by special test stripes. After 14 days the product must be disposed, even if the concentration is still superior to the MEC.

Mode of action

In the case of bacteria, OPA provokes the formation of crossed bonds between the cytoplasmic membrane lipoproteins with a subsequent cementation effect on the external layer of the cell and limitation of the exchanges. The periplasmic enzymes are also deactivated with consequent rapid death of the cell.

In the case of fungi and yeasts, the main interaction site is the chitin, principle component of the cellular wall, as well as the superficial enzymes present in the cellular membrane. As with glutaraldehyde, OPA is not effective against biofilm.

Spectrum of activity

OPA is capable of performing a rapid disinfection action in just 5 minutes at room temperature (20°C) on the majority of tested microorganisms, with the exception of spores for which higher concentrations and contact times (1% for 10–12 hours or 0.55% for 24 hours) are required.

Specifically, in laboratory, it is effective in:

- 5 minutes against bacteria in vegetative form (e.g. *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella choleraesuis, Enterococcus, Escherichia coli*).
- 5 minutes against viruses (*Adenovirus, Coxsackie virus, Citomegalovirus, Herpes simplex, HIV-1,* Human *Coronavirus, Influenza* Type A, *Poliovirus, Rhinovirus*),
- 5 minutes against yeasts, fungi and moulds (*Candida albicans, Aspergillus niger* and Trichophyton mentagrophytes),
- 5 minutes against *Mycobacterium bovis, M. avium, M. terrae, M. smegmatis*,

- 10 hours against the spores *Clostridium difficile* and *Bacillus subtilis*.

Material compatibility

OPA has proved to be compatible with a wide range of materials commonly used in the production of re-usable medical devices (metal, plastic, elastomers and adhesives) and, in many cases, it was found to be less aggressive than glutaraldehyde. Endoscopic instruments have undergone tests and are considered to be compatible with the solution. For prolonged contact times (greater than 15 minutes), the substrates with which it comes into contact can be subjected to permanent discolouring.

Toxicity/precautions

OPA is a molecule less volatile than glutaraldehyde and its toxicity, considering the same target organs, is of minor relevance.

Exposure to OPA has different effects according to the type of contact:

- Ingestion can cause irritation to the pharynx, esophagus and stomach with nausea, vomiting and diarrhoea.
- Skin contact can cause temporary blotches and slight irritations mainly after prolonged exposure. Such symptoms usually disappear when exposure is terminated.
- Eye contact can cause marks, excessive lachrymation and conjunctivitis.
- Inhalation: OPA is not considered volatile and is not thought to carry risks for inhalation during normal use. Exposure to spray or particulate can provoke, however, bland irritation to respiratory tracts with coughing and sneezing.

This product does not result to be mutagenic, embryotoxic or terotogenic in humans. Its components are not considered carcinogenic.

Occupational exposure limits have not, however, been established.

As with glutaraldehyde, the use of OPA also must

1. *Envisage the use of adequate personal protective equipment:*
   - protective eyewear,
   - authorized ventilators with filters for organic vapours, only in the presence elevated vapour concentrations,
   - protective smock,
   - butyl or nitrile gloves or a double pair of latex gloves.

2. *Envisage use in a ventilated environment and in closed containers* (if these requisites are satisfied, extraction systems are not necessary).

3. Envisage staff training for correct usage and relative information regarding toxicity.

In case of exposure, the same first aid measures for glutaraldehyde are valid:

http://dx.doi.org/10.5772/61219

- Eye contact: wash with plenty of water for at least 10 minutes. Remove contact lenses if possible to do easily. Visit the optician.
- Skin contact: remove contaminated clothes and wash the affected parts with soap and water. Consult a doctor if irritation persists.
- Ingestion: the product can cause ulceration and inflammation of the upper digestive system if ingested; it is preferable, therefore, not to cause vomiting but to resort to a cautious gastric lavage.
- Inhalation: transfer the person to a ventilated area. Artificial respiration may be necessary.

Disposal

According to Italian legislation, as with glutaraldehyde, disposal of the exhausted solution to sink is permitted, taking into account the high levels of dilution by water used daily for patient care. The sink must, however, be in a well-ventilated environment and disposal should be followed by running water to accelerate the discharge. The disposal of large quantities directly into the sewers can, however, cause damage to the purification system through the inhibition of bacterial activity.

Indications for use

0.55% OPA is indicated for the high-level disinfection of endoscopes and semi-critical medical devices with a contact time of at least 5 minutes at a temperature of 25°C in an AER and 12 minutes at 20°C in a manual immersion system.

Rinsing for at least 1 minute with copious water is sufficient to remove all traces of the disinfectant.

14.3. Peracetic acid (e.g. Nu Cidex, Steris, Persafe, Gigasept, Adaspor, Oxydrox, Perax liquid, Steradrox, Anioxide, SP3) [31, 32]

Active ingredient

Peracetic acid solutions are colourless or slightly yellow aqueous solutions, with a pungent odour and pH of around 6, containing a mixture of hydrogen peroxide and acetic acid.

The peracetic acid solutions commonly used in the medical field are:

- diluted working solution from concentrates,
- working solutions prepared by automatic systems which control all variables (dilution, temperature, contact times and pH),
- prepared to a defined concentration (0.35%).

Characteristics

Peracetic acid is an unstable compound and therefore it is necessary to store the concentrated solutions in bottles, preferably in a cool environment. *The working solutions should be prepared*

and are valid from 1 hour to 12 days depending on the type of dilution, on the pre-cleaning procedure and on the minimum recommended concentration.

Mode of action

It has not been defined definitively; the activity seems to be linked to the strong oxidizing power both at the cellular membrane level of the microorganism (interruption of the chemiosmotic function) and inside the microbial cell (irreversible damage to the essential enzymatic system).

Being an oxidant, peracetic acid cleans and de-scales eventual deposits of the material.

Spectrum of activity

Peracetic acid is characterized by a rapid disinfection activity. A 0.35% solution in laboratory was seen to be effective in 10 minutes at room temperature against the following microorganisms:

- Bacteria in vegetative form (e.g. *Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus, Escherichia coli*).
- Viruses such as HCV, HIV, HBV, *Coronarovirus.*
- Yeasts, fungi and moulds (*Candida albicans*, *Aspergillus niger*).
- Mycobacterium such as *Mycobacterium tuberculosis*, *M. avium*, *M. terrae*, *M. smegmatis.*
- Spores of *Clostridium sporogenes*, *Bacillus subtilis*, *Bacillus cereus*.

Material compatibility

The activated solution demonstrates good compatibility with materials commonly present in medical devices, particularly endoscopes and AERs. It can cause discolouring of the insertion tube.

Toxicity/precautions

The concentrated solutions (>0.35%) and the peracetic acid vapours in contact with the skin and the mucous membranes can cause irritation, sometimes even severe; for this reason, it is necessary to rinse carefully all disinfected medical devices and wear appropriate personal protective equipment during handling:

- mask for acid vapours in case of emergency,
- protective gloves (neoprene or heavy rubber),
- protective eyewear,
- complete protective clothing.

The 0.15% commercial solutions are neither corrosive nor irritants (only slightly for the eyes).

The literature indicates TLV/TVA[2] values of 10 ppm.

In case of exposure, the following are required:

- Eye contact: wash with plenty of water for at least 10 minutes. Remove contact lens if possible to do easily. Visit the optician.
- Skin contact: remove contaminated clothes and wash with soap and water the affected parts of the skin. Consult a doctor if irritation persists.
- Ingestion: the product can cause ulceration and inflammation of the upper digestive system if ingested; it is preferable, therefore, not to cause vomiting but to resort to a cautious gastric lavage.
- Inhalation: transfer the person to a ventilated area. Artificial respiration may be necessary.

Disposal

Peracetic acid is not harmful and does not pollute the environment because it breaks down into acetic acid, water and oxygen.

Indications for use

Cartridges containing 35% peracetic acid inserted into a specific AER obtain, in controlled conditions, a 0.2% solution and operate at around 55°C with a contact time of 12 minutes. This does not seem to be a particularly suitable system for flexible endoscope reprocessing due to the cost of each cycle.

The stabilized and buffered 0.35% solution has, according to studies, the same indications, being effective in 5 minutes against bacteria, fungi, virus and mycobacterium and 10 minutes against spores. It should be prepared as a working solution and is stable for 24 hours. It can be used for up to 20 cycles or up to a concentration of not less than 2500 ppm.

Even though the solution contains anti-corrosion inhibitors, it is not recommended for use in AERs which contain aluminium or copper. Tests have demonstrated variations in the plating of rigid endoscopes which contain such metals.

The technical bulletin for the 0.15% stabilized solution indicates a contact time of 10–15 minutes for high-level disinfection and 30 minutes for sporicidal action. This solution must also be activated and disposed of every 24 hours.

As confirmed by the study carried out among the ENT departments, there are a variety of products marketed under the name of peracetic acid. The usage and the contact times vary according to the product and consequently it is necessary, to carefully follow the instructions supplied by the manufacturer, as well as verifying the compatibility of the product with the instruments which need to be disinfected.

14.4. Chlorine dioxide (e.g. ClO_2 Tristel) [26, 35, 36]

Active ingredient

A molecule composed of one atom of chlorine and two atoms of oxygen (ClO_2). The biocidal power of ClO_2 has long been recognized for use in different industrial applications and for the

2 Threshold limit value-time weighted average: average concentration of a chemical agent weighted on an exposure level of 8 hours and for 40 hours per week, to which operators may be exposed without adverse effects for their health being apparent.

disinfection of drinking water. The particular characteristic of this disinfectant is its broad spectrum of activity in rapid contact times at low levels of concentration. Its oxidizing capacity is the equivalent of 2.5 times that of chlorine. It can be used in manual systems, electronically controlled manual systems and also automatic systems.

Characteristics

ClO_2 is an unstable gas, it cannot be transported and therefore *must be generated at the moment of use*. The patented Tristel method envisages generation by means of mixing a sodium chlorite solution with a mixture of organic acids, prevalently citric acid. The almost instantaneous reaction between the two precursors produces chlorous acid, which in turn dissociates to release a ClO_2 gas in solution for immediate use at a level of concentration suitable for the sporicidal disinfection of semi-critical medical devices. The concentration of ClO_2 (read by spectrophotometry immediately at the end of the activation time) in the wipes system is 175–225 ppm (approximately 0.02%) while the diluted liquid format for immersion is 50–60 ppm (0.005–0.006%).

Mode of action

ClO_2 reacts almost instantaneously with of all types of microorganisms, creating an electron transfer to form a breach in the surface from which all vital constituents pour out of the microorganism with consequent destruction by lysis. The particular means of microbial destruction prevents bacteria, fungi and viruses developing resistance to the molecule and creating mutant strains.

Spectrum of activity

The ClO_2 activity in its different formulations has been tested microbiologically in laboratories according to the European norms EN 14885 to demonstrate its effectiveness.

It is effective *in 30 seconds in the ready–to-use format and in 5 minutes in the diluted liquid format for immersion on the following microorganisms*:

- Spores (e.g. *Bacillus subtilis* and *Clostridium difficile*),
- Mycobacterium (e.g. *M. tuberculosis*, *M. avium* e *M. terrae*),
- Viruses (e.g. HBV, HCV, HIV, *Poliovirus* Type 1, *Adenovirus*, *Orthopoxvirus*),
- Fungi (e.g. *Candida albicans*, *Aspergillus niger*),
- Bacteria (e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus*).

Material compatibility

Instrument integrity is guaranteed when used with single-use ClO_2, providing the instructions are followed: *no damage has ever been noted from using the wipes system, neither after extensive laboratory testing nor after a decade of use in the field.*

Toxicity/precautions

http://dx.doi.org/10.5772/61219

The safety for people using ClO_2 has been confirmed by toxicological studies performed on both humans and animals. The results demonstrated that at the concentrations used there are no reactions or contraindications. It is however recommended to use gloves during handling.

Disposal

The solution of ClO_2 decomposes into a simple saline solution and consequently has no negative impact on the environment and does not entail additional disposal costs.

Indications for use

ClO_2 *is indicated for the high-level disinfection of endoscopes and semi-critical medical devices. The formulation used in the wipes system is ready to use with a contact time of 30 seconds, while the diluted liquid formulation has a contact time of 5 minutes.*

There is only one dilution with water at room temperature and pH adjustment is unnecessary.

14.5. Glucoprotamin (e.g. Sekusept Plus, Sekumatic) [36]

Active ingredient

Glucoprotamin is a substance with a wide spectrum of activity obtained from the reaction of glutamic acid and coco alkyl propylene diamine. Both precursors are natural compositions and therefore highly biodegradable.

Characteristics

A clear aqueous solution, yellow in colour, not volatile, which must be diluted in water from 1–4% without the necessity of additional activators. It is usable in both manual and automatic systems.

The solution is valid for 14 days.

Mode of action

Glucoprotamin operates by disrupting the cell membrane, by inhibiting the activity of the principle enzymes and denaturing the cell proteins.

Spectrum of activity

Glucoprotamin has a wide spectrum of activity against bacteria (including mycobacterium), yeast and fungi, enveloped viruses and partially effective against non-enveloped viruses. It acts specifically on the following microorganisms:

- Bacteria (tested on *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Micrococcus luteus, Enterococcus hirae, Gemella morbillorum, Corynebacterium* spp.),
- Mycobacterium (tested on *M. tuberculosis*, *M. avium* and *M. terrae*),
- Viruses (tested on HIV, HBV, HCV),
- Yeasts (tested on *Candia albicans*).

The contact time for bacteria is 5 minutes and 15 minutes for yeasts.

Material compatibility

The product has been tested and approved for use on Olympus and Storz endoscopes, Rusch anesthesia materials and Martin instruments.

Toxicity/precautions

Health risks: eye irritation.

The literature indicates TLV/TVA[3] values of 500 ppm.

Respiratory tract protection: none, in normal usage conditions.

Hand protection: wear protective gloves in nitrilic or butylic rubber.

Eye protection: wear protective eyewear.

Skin protection: none, in normal usage conditions.

In case of exposure, the following first-aid measures should be adopted:

- Eye contact: wash with plenty of water for at least 10 minutes. Remove contact lens if possible to do easily. Visit the optician.
- Skin contact: remove contaminated clothes and wash with soap and water the affected parts of the skin. Consult a doctor if the irritation persists.
- Ingestion: the product can cause ulceration and inflammation of the upper digestive system if ingested; it is preferable, therefore, not to cause vomiting but to resort to a cautious gastric lavage.
- Inhalation: transfer the person to a ventilated area. Artificial respiration may be necessary.

Disposal

The discharge of the product into the water network is damaging to microflora, microfauna and aquatic organisms for a brief period.

According to Italian legislation, disposal of the exhausted solution to sink is permitted, considering the high levels of dilution by water used daily for patient care. The sink must, however, be in a well-ventilated environment and disposal should be followed by running water to accelerate the discharge.

Indications for use

Glucoprotamin is indicated for the high-level disinfection and simultaneous detersion of flexible endoscopes, anaesthesia materials and semi-critical medical devices.

---

3 Threshold limit value-time weighted average: average concentration of a chemical agent weighted on an exposure level of 8 hours and for 40 hours per week, to which operators may be exposed without adverse effects for their health being apparent.

http://dx.doi.org/10.5772/61219

Glucoprotamin has been taken into consideration because its usage in some ENT departments was found in the survey findings. Evaluation studies of its microbial efficacy currently available indicate a wider spectrum of activity than intermediate disinfectants, but its efficacy against spores, a fundamental requisite for a high-level disinfectant, is not documented. Further research is necessary in order to confirm its use for the reprocessing of endoscopes.

15. Conclusions

15.1. General norms

1. Every patient should be considered a potential source of infection and consequently, each examination and all reprocessing procedures must be performed with the same accuracy.
2. The responsibility of the disinfection process is attributed to the nursing staff and the doctor using the instrument.
3. The choice of disinfection systems should be made in agreement between the head of the operating unit, the hospital pharmacy and the hospital infection control committee.
4. Staff should wear personal protective equipment during the endoscopic procedure and in the various phases of reprocessing of the instrument.
5. Contaminated and clean areas should be distinctly divided.
6. Disinfection should be performed by adequately trained staff, whose competence is periodically checked.
7. Periodic microbiological controls are not advisable as an indicator of the disinfection process. In case of suspected contamination, endoscope, tap water and instruments used in the disinfection process should be microbiologically tested.
8. When there is a suspected or ascertained case of infection, consult the hospital infection control committee.

15.2. Reprocessing steps

1. After the endoscopic exam, a leak test and a visual check of the integrity of the instrument should be performed before reprocessing.
2. Endoscopes which cannot be completely immersed should be substituted.
3. Before using the pre-clean or disinfection solution, consult the technical bulletin and the safety data sheet: concentration levels, temperature, contact time should be respected in order to achieve an effective disinfection.
4. The thorough cleaning of the instrument (immediately after use) with a detergent solution in order to remove soil and organic material is fundamental for a successful disinfection.

5. The disinfectant should be registered with the Health Ministry and the registration includes the indication of how to use, the concentrations, contact time, temperature and pH.

6. In the case of the disinfectant being reusable, it is necessary to:

   - Test the MEC of the disinfectant at the beginning of each working day. The results should be documented and the solution should be disposed if the concentration is below the minimum required.

   - Dispose of the disinfection liquid at the end of the period indicated for use without taking into account the MEC.

7. Rinse the endoscope according to indications and dry before storing. The humidity increases the risk of infections.

8. Keep a register of the endoscope usage and of the management and disinfection of eventual AERs.

15.3. Disinfection systems

The ideal disinfection system should allow

- standardization of the process, to reduce the possibility of error,
- rapid turnaround of endoscopes,
- reduction of risks of operator contamination,
- reduction of risks of damage to endoscopes.

Advantages and disadvantages of the various disinfection systems are indicated so that everyone can choose the one most adaptable to their local situation (human and economic resources, available space, volume of activity, number of endoscopes).

1. Manual immersion systems do not require big investments but have the following disadvantages:

- risks of errors or forgetfulness,
- inadequate “traceability”,
- risk of operator contamination,
- risk of environmental contamination,
- damage to endoscopes,
- disinfection times of at least 20 minutes.

2. AERs:

- standardized process which avoids errors or forgetfulness,

http://dx.doi.org/10.5772/61219

- allows "traceability" of the process,
- reduces possible operator contact with contaminated instruments,
- reduces the possibility of environmental contamination,
- reduces risk of damage to endoscopes.

Possible disadvantages:

- equipment and maintenance costs,
- adequate space for installation of equipment (often at a distance from the endoscopic room with consequent loss of time due to transport and the increased risk of damage to the instrument during transport),
- time required for the disinfection process (normally at least 20 minutes). Added to transport times, the endoscope may not be available before 1 hour.

Some manufacturers produce AERs specifically for ENT endoscopes, smaller than those used for gastroenterology, easier to locate and at lower cost.

3. The wipes system using ClO_2

- allows a rapid rotation of the instrument (less than 5 minutes),
- allows traceability because the wipes are single use.

Although easy to use, the system is manual and therefore requires careful and continuous staff training to ensure that the procedure is performed correctly.

4. Manual immersion system with microprocessor:

- guarantees the contact time and avoids over exposure to chemistry which can potentially damage the instrument,
- allows traceability,
- has lower purchase and maintenance costs compared to AERs.

The pre-clean step and the rinse step are both manual and therefore require care.

5. Sterile protective sheaths:

allow a rapid rotation of the instrument, but the correct usage envisages cleaning and disinfection after sheath removal.

Disadvantages include

- possible discomfort for the patient,
- optical part of the endoscope not protected against contamination,
- possible rupture of the sheath during patient visit,
- possible damage to the endoscope when removing the sheath,

- hampered visuals,
- cost.

The choice of the disinfection system is made in consultation with the Director of the Unit, the Pharmacy Service and the Infection Control Task.

The nursing staff as well as the doctor using the endoscope are responsible for the disinfection process and must be adequately trained.

Author details

Matteo Cavaliere* and Maurizio Iemma

*Address all correspondence to: matorl@inwind.it

Department of Otorhinolaryngology, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

References

[1] American Society for Gastrointestinal Endoscopy (ASGE). Technology Assessment Committee Position Paper. Transmission of infection by gastrointestinal endoscopy. Gastrointest Endoscopy 1993;36:885–8.

[2] Birnie GC, Quigley A, Clements GB, et al. Endoscopic transmission of hepatitis B virus. Gut 1983;24:171–4.

[3] Bronowicki JP, Venard V, Botte C. Patient-to-patient transmission of hepatitis C virus during colonoscopy. N Engl J Med 1997;337:237–40.

[4] Morris J, Duckworth GJ, Ridgway GL. Gastrointestinal endoscopy decontamination failure and the risk of transmission of blood-borne viruses: a review. J Hosp Infect 2006;63:1–13.

[5] Agenzia Sanitaria Regionale dell'Emilia-Romagna. Reprocessing degli endoscopi. Indicazioni operative. Dossier 133, Bologna; 2006.

[6] Heeg P. Reprocessing endoscopes: national recommendations with a special emphasis on cleaning. The German perspective. J Hosp Infect 2004;56:S23–6.

[7] CDC. Guideline for Disinfection and Sterilization in Healthcare Facilities. University of North Carolina, Chapell Hill; 2008.

[8] CDC. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. University of North Carolina, Chapel Hill; 2004.

http://dx.doi.org/10.5772/61219

[9] CCLIN Sud-Ouest-Centre de coordination de lutte contre les infections nosocomiales. Prevéntion du risque infectieux en imagerie médicale non interventionnelle. Bordeaux 2004.

[10] Culver DA, Gordon SM, Mehta AC. Infection control in the bronchoscopy suite. Am J Respir Crit Care Med 2003;167:1050–6.

[11] Rutala WA, Weber DJ. Reprocessing endoscopes: United States perspective. J Hosp Infect 2004;56(2):27–39.

[12] Spaulding EH. Chemical disinfection of material and surgical materials. In: Block SS (ed.) Disinfection, Sterilization and Preservation. Philadelphia: Lea & Febiger; 1968, pp. 617–641.

[13] APIC Guidelines Committees. APIC Guideline for infection prevention and control in flexible endoscopy. Am J Infect Control 2000;28:138–55.

[14] Beilenhoff U, Neumann CS, Biering H, et al. ESGE/ ESGENA guideline for process validation and routine testing for reprocessing endoscopes in washer disinfectors, according to European Standard EN ISO 15883 parts 1,4 and 5. Endoscopy 2007;39:85–94.

[15] Isomoto H, Urata M, Kawazoe K, et al. Endoscope disinfection using chlorine dioxide in an automated washer-disinfector. J Hosp Infect 2006;63:298–305.

[16] Coates D. An evaluation of the use of chlorine dioxide (Tristel One-Shot) in an automated washer/disinfector (Medivator) fitted with chlorine dioxide generator for decontamination of flexible endoscopes. J Hosp Infect 2001;48:55–65.

[17] Alvarado CJ, Anderson AG, Maki DG. Microbiological assessment of disposable sterile endoscopic sheaths to replace high-level disinfection in reprocessing: a prospective clinical trial with nasopharyngoscopes. Am J Inf Control 2009;37:408–13.

[18] Baker KH, Chaput MP, Clavet CR, et al. Evaluation of endoscope sheaths as viral barriers. Laryngoscope 1999;109:636–9.

[19] Awad Z, Pothier DD. A potential danger of flexible endoscopy sheaths: a detached tip and how to retrieve it. J Laryngol Otol 2009;123:243–4.

[20] Martin Y.H., Floss H., Zuhlsdorf B. The importance of cleaning for the overall results of processing endoscopes. J Hosp Infect 2004;56:S16–22.

[21] Schembre DB. Infectious complications associated with gastrointestinal endoscopy. Gastrointest Endosc Clin N Am 2000;10:215–31.

[22] Ippolito G, Petrosillo N, Suzzi R. Rischio di trasmissione iatrogena e nosocomiale dell'agente della malattia di Creutzfeldt-Jakob e misure di prevenzione. GIIO 1997;4(2):66-71

[23] OMS World Health Organization. Infection control guidelines for transmissible spongiform encephalopathies. 2000.

[24] Beilenhoff U, Neumann CS, Rey JF, et al. ESGE-ESGENA guideline for quality assurance in reprocessing: Microbiological surveillance testing in endoscopy. Endoscopy 2007;39:175–81.

[25] ECRI. Healthcare Product Comparison System. Duodenoscopes; Gastroscopes; Choledoscopes 2004;2:1–10.

[26] Society of Gastroenterology Nurses and Associates. Guidelines for the use of high-level disinfectants and sterilants for reprocessing of flexible gastrointestinal endoscopes. Gastroenterol Nurs 2004;27(4):198–206.

[27] Agolini G, Raitano A, Vitali M. Glutaraldeide, una saga tutta italiana. View & Review, 1999;7:7–15.

[28] Scott E., Gorman S. Glutaraldeyde. In: Block SS (ed.). Disinfection, Sterilization and Preservation. Philadelphia, Lippincott Williams & Wilkins, 2001.

[29] McDonnel G, Pretzer D. New and developing chemical antimicrobials. In: Rutala WA, Weber DJ and the Healthcare Infection Control Practices Advisory Committee. (eds.). Draft Guideline for Disinfection and Sterilization in Healthcare Facilities. CDC, 2002.

[30] Rutala WA, Weber DJ. Disinfection of endoscopes: review of new chemical sterilants used for high-level disinfection. Infect Control Hosp Epidemiol 1999;20(1):69–76.

[31] Curti C. Una gestione razionale dei principi attivi usati per la disinfezione/sterilizzazione ospedaliera; schede monografiche: Acido peracetico. In: Raitano A, Curti C, Agolini G. (eds.) Igiene e disinfezione clinica nelle strutture ospedaliere. Principi e tecniche applicate per gli anni 2000. Edizioni Kappadue, 2002.

[32] Malchesky PS. Medical application of peracetic acid. In: Block SS. (ed.). Disinfection, Sterilization and Preservation. Philadelphia, Lippincott Williams & Wilkins, 2001.

Chapter 2

Anesthesia Innovations for Endoscopy of Gastrointestinal Tract

Somchai Amornyotin

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60730

Abstract

Gastrointestinal endoscopy (GIE) is a procedure for diagnosis and treatment of gastrointestinal tract abnormalities. This procedure requires some forms of anesthesia. The goal of procedural anesthesia is safe, effective control of pain and anxiety, as well as an appropriate degree of memory loss or reduced awareness. Generally, the majority of GIE procedures are performed by using topical anesthesia and intravenous sedation. General anesthesia is carried out in long and invasive procedures such as endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, and small bowel enteroscopy, as well in patients with history of failed sedation or drug and substance abuse, uncooperative or pediatric patients, and patients with cardiorespiratory system instabilities. The appropriate anesthetic agents for GIE procedures could be short acting, rapid onset with little adverse effects and also improved safety profiles. To date, the new anesthetic drugs and monitoring equipments for safety and efficacy are available. The present review focuses on pre-anesthetic assessment, anesthetic drugs used, monitoring practices, and post-anesthesia care for anesthesia innovations in GIE procedures.

Keywords: Anesthesia, Innovation, Gastrointestinal endoscopy, Safety, Efficacy

1. Introduction

Anesthesia is one of the important components of gastrointestinal endoscopic (GIE) procedures. The aim of anesthesia for these procedures is to improve patient's comfort and endo-

scopic practice as well as patient and endoscopist satisfaction. The requirement for anesthesia is dependent on the type and duration of endoscopy, experience of endoscopist, and patient's physical status. The anesthetic regimens for GIE procedures are quite different. Several guidelines from American Society of Anesthesiologists (ASA) [1] and American Academy of Pediatrics [2] are established. Appropriate pre-anesthetic assessment, anesthetic drugs used, monitoring practices and post-anesthesia care for anesthesia in GIE procedures are essential.

1.1. Pre-procedure assessment

All patients scheduled to receive anesthesia/sedation should have a history and appropriate physical examination. Several risk factors including history of obstructive sleep apnea, alcohol or drug abuse, and history of adverse reaction to previous anesthesia/sedation are investigated. The patient physical status should be classified according to the ASA. The pregnancy test is recommended in women of childbearing age [3]. Consequently, written consent should be obtained. An anesthesia consultation should be done in high-risk patients including patients with respiratory or hemodynamic instability, obstructive sleep apnea, and high-risk airway management, as well as patients with ASA physical status >III and history of anesthesia-related adverse events.

2. Monitoring

Cardiorespiratory-related adverse events are a leading cause of morbidity and mortality associated with GIE procedures. Continuous monitoring of anesthetized patients is very important for safety. The physicians need to monitor the patients' status throughout the procedure. Clinical observations including pattern of respiration, skin or mucosa color, and level or depth of anesthesia are continuously observed.

2.1. Pulse oximetry

Pulse oximetry is a noninvasive device for continuous measurement of arterial oxygen saturation. Because clinical observation alone is inaccurate in the detection of hypoxemia, pulse oximetry has become a standard of care during GIE procedures. Oxygen saturation levels under 90% must be treated. However, pulse oximetry and oxygen supplementation do not diminish the severity or incidence of cardiorespiratory complications. In addition, oxygen desaturation is relatively a late sign [4].

2.2. Capnography

Moreover, pulse oximetry and clinical observation cannot detect the development of hypercapnea. Capnography has been utilized to permit the safe titration of propofol by a qualified gastroenterologist during invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS).

http://dx.doi.org/10.5772/60730

2.3. Noninvasive blood pressure

Blood pressure and heart rate are important parameters of cardiovascular monitoring. The alterations of blood pressure are mediated by the depressive effects of anesthetic agents. Baseline hemodynamic parameters also provide useful information of the effects of various medical conditions. Generally, blood pressure and heart rate will be documented before anesthesia, and at least 5 min for deep sedation and general anesthesia, as well as every 15 min for mild and moderate sedation. Blood pressure is more likely to predict increasing and decreasing doses of anesthetic drugs.

2.4. Electrocardiography

The use of electrocardiography (ECG) was aimed to detect cardiac arrhythmias in high-risk patients undergoing anesthesia. However, the use of ECG during GIE procedure remains controversial [6]. American Society for Gastrointestinal Endoscopy (ASGE) and ASA practice guidelines recommend the use of ECG during GIE anesthesia in patients with significant cardiovascular diseases or arrhythmias. However, ECG is not recommended for routine use of ECG in patients with ASA physical status I or II [1, 4, 7].

2.5. Other monitors

Other monitors such as invasive arterial blood pressure, central venous pressure (CVP), and pulmonary arterial catheterization (PAC) are infrequently used during GIE anesthesia. However, these invasive monitors should be used in some high-risk patients including patients with severe hemodynamic instabilities and patients with shock.

2.6. Bispectral index monitoring

The depth of anesthesia cannot be reliably judged by clinical assessments alone. Currently, the Bispectral (BIS) index has been reported to be more accurate in measurement of the depth of anesthesia. The BIS scale ranges from 0 to 100 (0, no cortical activity or coma; 40-60, unconscious; 70-90, varying levels of conscious sedation; 100, fully awake). In the past, BIS monitor was used to assess the patient consciousness during general anesthesia [4, 8]. To date, its use has subsequently expanded into the procedural sedation technique. However, the use of BIS during GIE procedures remains a controversial issue.

The usefulness of BIS monitoring for GIE procedure was confirmed by the study of Bower and colleagues. This study showed the correlation of BIS index and the Observer's Assessment of Alertness/Sedation (OAA/S) scale for sedation during GIE procedures. It also suggested that a bispectral index near 82 corresponded with acceptable sedation level for GIE procedure [9]. Al-Sammak and coworkers compared BIS with clinical assessment for sedation during ERCP procedure in pediatric patients. The duration of sedation, recovery period, patient satisfaction, and total dose of sedative agents in the BIS group were better than in the clinical assessment group. This study demonstrated that BIS might be a valuable monitor for safe level of sedation and endoscopist's satisfaction during ERCP [10]. Another study also showed that BIS moni-

toring guided to a decrease in the propofol dose for sedation in ERCP procedures. Mean BIS values throughout the procedure and during the maintenance period of sedation were 61.68 ± 7.5 and 53.73 ± 8.67, respectively [11].

In contrast, several reports demonstrated that BIS index had low accuracy for detecting deep sedation and it was not helpful for titrating propofol to an adequate depth of sedation level. For example, Chen and Rex evaluated the utility of BIS as a monitoring device for nurse-administered propofol sedation (NAPS) during colonoscopic procedure. The study showed the mean time required to accomplish BIS values ≤60 was significantly longer than the mean time required to achieve an Observer's Assessment of Alertness/Sedation score of 1 (deep sedation). Additionally, there was also a lag time between the time required from the last dose of propofol and the time returned to baseline. The authors concluded that BIS index was not a useful device in titrating propofol to an adequate depth of sedation level [12].

Drake and coworkers also confirmed that BIS did not lead to the reduction in mean propofol dose or recovery time when used for sedation in colonoscopy [13]. Moreover, an observational study also showed that BIS index had a low accuracy for detecting deep sedation because of an overlap of scores across the sedation levels. Further improvements in BIS are needed to differentiate deep from moderate sedation for GIE procedures [14].

2.7. Narcotrend™

Narcotrend™ accomplishes a computerized analysis of the raw EEG. A statistical algorithm is used for analysis, resulting in a six-stage classification from A (awake) to F (general anesthesia/coma) and 14 substages [4, 15]. Wehrmann and colleagues evaluated 80 patients who underwent ERCP procedures by using EEG monitoring and clinical assessment for sedation. Their study demonstrated that mean propofol dose, decrease in blood pressure, and recovery time in the EEG monitoring group were significantly lower than in the clinical assessment group. The authors confirmed that EEG monitoring permitted more effective titration of propofol dosage for sedation during ERCP procedures and was associated with more rapidly patient recovery [16].

My previous study used the Narcotrend™ to guide the depth of sedation for ERCP procedure. Narcotrend™ monitoring was an effective tool for maintenance of the depth of sedation level in this procedure [17]. The other study compared the clinical efficacy of Narcotrend™ monitoring and clinical assessment used to provide deep sedation in patients who underwent ERCP procedure. In the study, Modified Observer's Assessment of Alertness/Sedation scale 1 or 2 and the Narcotrend™ index 47-56 to 57-64 were maintained during the procedure. All endoscopies were completed successfully. Both Narcotrend™ and clinical-assessment-guided propofol deep sedation were equally safe and effective as well as demonstrated comparable propofol dose and recovery time. However, the Narcotrend™-guided sedation showed lower hemodynamic changes and fewer complications compared with the clinical-assessment-guided sedation [18].

http://dx.doi.org/10.5772/60730

3. Anesthetic technique

3.1. Topical anesthesia

Esophagogastroduodenoscopy (EGD) is commonly performed by using topical pharyngeal anesthesia. Topical lidocaine is normally used as pretreatment for pharyngeal anesthesia. My previous study evaluated the clinical efficacy of topical viscous lidocaine solution and lidocaine spray when each was used as a single agent for unsedated EGD [19]. All patients were randomized into the viscous lidocaine (V) group (n = 930) or the lidocaine spray (S) group (n = 934). The results showed the procedure was successfully completed in 868 patients from group V and 931 patients from group S. Patient's and endoscopist's satisfaction, pain score, patient tolerance, and ease of intubation in group S were significantly better than those in group V. Additionally, adverse events in group S also occurred significantly lower than group V. This study demonstrated that the use of topical lidocaine spray was shown to be a better form of pharyngeal anesthesia than viscous lidocaine solution in unsedated EGD procedure [19].

Consequently, the use of posterior lingual lidocaine swab can apply for EGD procedure. Soweid and colleagues evaluated the effect of posterior lingual lidocaine swab in 80 patients who underwent diagnostic EGD procedures on patient tolerance, the ease of performance of EGD procedure, and to determine if such use would decrease the need for intravenous sedation [20]. The result of their study demonstrated that patients in the lidocaine swab group tolerated the procedure better than those in the lidocaine spray group. The procedural difficulty and the need of intravenous sedation in the lidocaine swab group were lower than in the lidocaine spray group. Additionally, the patients and the endoscopists in the lidocaine swab group were more satisfied than in the lidocaine spray group. They suggested the use of posterior lingual lidocaine swab for EGD procedure because of patient comfort and tolerance, endoscopist satisfaction, and reduction of the need for intravenous sedation.

Ramirez and coworkers also compared the effect of glossopharyngeal nerve block and topical anesthetic agent for EGD procedure [21]. The aim of the study was to evaluate the sedation, tolerance to the procedure, hemodynamic stability, and the adverse events. They performed a clinical trial in a total of 100 patients who underwent EGD procedures. All patients in both arms also received intravenous midazolam. The procedures were reported without discomfort in 48 patients (88%) in the glossopharyngeal nerve block group and 32 patients (64%) in the topical anesthetic group. There were no significant differences in the incidence of nausea and retching in both groups. The study confirmed that the use of glossopharyngeal nerve block provided greater patient comfort and tolerance as well as also diminished the need for sedation in EGD patients [21].

3.2. Intravenous sedation

Sedation for GIE procedure can be safely and effectively performed with a multidrug regimen utilizing anesthesiologist or nonanesthetic personnel with appropriate monitoring. Currently, sedation practices for GIE procedures vary widely. The need for sedation is decided by the

type of endoscopy, duration of procedure, degree of endoscopic difficulty, patient physical status, and physician's preferences. However, the sedation regimen for GIE procedures is still varied. Benzodiazepines and opioids are commonly used by nonanesthetic personnel. In contrast, propofol in combination with opioids and/or benzodiazepines is usually used by anesthetic personnel.

3.3. General anesthesia

The choice of anesthetic technique for GIE procedure depends on the patient and the type of procedure. General anesthesia is commonly utilized in patients with ASA physical status >III and patients with cardiorespiratory instability, as well as in long duration and complicated procedures. Traditionally, tracheal intubation is also performed when general anesthesia is used. An anesthesiologist usually uses balanced anesthesia technique including opioid, inhalation agent, and neuromuscular blocking drug. The majority of these anesthetic agents have short-acting and short-duration properties.

4. Anesthesia innovative techniques

4.1. Target-controlled infusion

Target-controlled infusion (TCI) is a computer-controlled open-loop administration of anesthetic drugs. A continuous infusion technique uses a pharmacokinetic model to predict the patient plasma and effect site concentrations from the infusion design and allows the anesthesiologist to target a selected concentration. The device computes the appropriate infusion system to accomplish this concentration [22]. The TCI rapidly attains and maintains a predefined plasma or effect site concentration of the anesthetic drug. An appropriate target concentration for achieving the desired clinical endpoint is selected. The TCI delivery system performs better than the manual system. Presently, TCI devices for propofol administration are approved in several countries.

Mazanikov and colleagues compared TCI (initial targeted effect-site concentration 2 mcg/mL) with patient-controlled sedation (PCS) (single bolus 1 mL, lockout time set at zero) in 82 patients who underwent elective ERCP procedures. Alfentanil was supplemented if needed. All procedures were performed successfully. Mean consumption of propofol and the recovery time in the TCI group was significantly greater than in the PCS group. However, mean consumption of alfentanil in both groups was comparable. The authors concluded that there were no benefits of TCI over PCS for propofol administration in ERCP procedures [23].

4.2. Patient-controlled sedation

Because of interindividual variability, new techniques of administration for sedation have been developed. Patient-controlled sedation (PCS) devices deliver a predefined bolus of intravenous drug during a defined time with or without a lockout interval. A prospective, randomized, controlled study compared the use of PCS with propofol and remifentanil and the

http://dx.doi.org/10.5772/60730

anesthesiologist-administered propofol sedation for 80 elective ERCP patients. Sedation level was assessed every 5 min by using Ramsay and Gillham sedation scores. All ERCP patients were completely successful except two patients in the PCS group. Mean level of sedation and total propofol consumption in the PCS group were significantly lower than in the anesthesiologist-administered propofol group. However, patient and endoscopist satisfaction were equally high in both groups. The study confirmed that PCS with propofol and remifentanil was a safe and well-accepted sedation technique for ERCP patients [24].

Moreover, the use of PCS with propofol and remifentanil has been compared with fentanyl and midazolam for sedation in patients who underwent colonoscopy by Mandel and colleagues [25]. Their study demonstrated that time to sedation and the recovery time in the PCS with the propofol and remifentanil group were significantly shorter than in the PCS with the fentanyl and midazolam group. However, the perceptions of patients, nurses and endoscopists were comparable between the two groups.

Procedural sedation in cirrhotic patients is challenged. Titration of sedative and analgesic drugs is needed for an optimal sedation level. The use of PCS for sedation in these patients is an alternative technique. Although, dexmedetomidine is suggested for procedural sedation and reported effective for alcohol withdrawal, the efficacy of dexmedetomidine as a sole anesthetic agent is controversial. Mazanikov and coworkers evaluated 50 patients with chronic alcoholism scheduled for elective ERCP procedures. All patients in the PCS with propofol and alfentanil group were successfully sedated, and in 19 of 25 (76%) patients in the dexmedetomidine group. They also suggested that a loading dose of dexmedetomidine 1 mcg/kg over 10 min, followed by continuous intravenous infusion 0.7 mcg/kg/h was insufficient for the ERCP procedure. In addition, dexmedetomidine was also related with prolonged recovery [26].

4.3. Computer-assisted personalized sedation system

The use of propofol for sedation in GIE procedures may allow for better quality of sedation and faster recovery. Computer-assisted personalized sedation system (CAPS) is based on the patient response to stimulation and physiologic profiles. It presents an attractive means of delivering safe and effective doses of propofol. The closed-loop target-controlled system or continuous EEG recordings are used to assess the degree of sedation. Patient-controlled platforms may also be used. These devices may help physicians titrating propofol administration and controlling the physiological functions [27].

The SEDASYS System is a CAPS integrating propofol delivery with patient monitoring to allow physicians to safely administer propofol. The efficacy and safety of this system for sedation during GIE procedures was evaluated and compared with the combination of benzodiazepine and opioid in 1000 adult patients with ASA physical status class I-III. All patients were sedated in mild to moderate depth of sedation level. The study demonstrated that SEDASYS system was safe and effective for sedation during EGD and colonoscopic procedures. Additionally, patient and physician satisfaction as well as recovery time in the SEDASYS group were significantly better than patients in the combination of benzodiazepine and opioid group [28].

The use of inadequate sedative agents results in over and under depth of sedation. The use of CAPS for administration of propofol by nonanesthetic personnel achieving mild to moderate sedation in patients who underwent GIE procedures was evaluated by Pambianco and coworkers [29]. This study showed that propofol administration in mild or moderate sedation level by nonanesthetic personnel used with CAPS system in patients who underwent EGD and colonoscopic procedures was safe and effective. Moreover, low propofol dosage and short recovery time were noted.

4.4. Closed-loop administration of anesthesia

Closed-loop administration of anesthesia systems can provide anesthesia automatically and its effect feedback controlled. This system contains a central system, a target control device such as syringe pump, vaporizer, and other drug delivery systems [30]. Currently, there are several closed-loop administration systems for neuromuscular blockade, depth of anesthesia, and pain control during decreased levels of consciousness. In addition, McSleepy is also a closed-loop control system that displays the patient's depth of consciousness, muscular movement during surgery, and the level of pain [30].

4.5. Teleanesthesia

Teleanesthesia is the use of telemedicine technology in anesthetic management including preoperative assessment at distance, video consultation, and performing anesthesia in remote locations where experienced anesthesiologists are not always present [30, 31]. The impact of telemedicine pre-anesthesia evaluation on periprocedural processes was confirmed by Applegate II and colleagues. Their study demonstrated that telemedicine pre-anesthesia evaluation offered patients time- and cost-saving benefits without more surgical delay. Moreover, telemedicine and in-person assessments were comparable, with high patient and physician satisfaction [32].

5. Anesthetic agents

5.1. Local anesthetic agents

Generally, lidocaine is the most common local anesthetic agent used for GIE procedure. The viscous lidocaine solution and lidocaine spray are usually performed for upper GIE procedure. In addition, lidocaine gel or jelly is frequently employed for lower GIE procedure. Recently, lidocaine lozenge has been tried to use for EGD procedure. Mogensen and colleagues evaluated the effect and acceptance of a lidocaine lozenge compared with a lidocaine viscous oral solution as pharyngeal anesthesia before EGD [33]. The 110 adult patients were randomized to receive either 100 mg lidocaine as a lozenge or 5 mL lidocaine viscous solution 2%. Supplemental intravenous midazolam was administered if needed. They concluded that the lozenge could reduce gag reflex and patients' discomfort, and improved patients' acceptance during the procedure. In addition, the lozenge form had also a good taste [33]. Another study of the lidocaine lozenge used for pharyngeal anesthesia in EGD procedure has been reported by

http://dx.doi.org/10.5772/60730

Tumminakatte and Nagaraj [34]. The authors compared the efficacy, safety, and patient comfort for the lidocaine lozenge and lidocaine viscous as a single agent before EGD procedure. This study showed that lidocaine lozenge was effective and safe for pharyngeal anesthesia before EGD procedure. It was relatively better than lidocaine viscous in terms of lesser discomfort and procedural difficulty as well as increased tolerability of the EGD procedure [34].

Moreover, topical bupivacaine could be used as pretreatment for pharyngeal anesthesia in unsedated EGD. The effect of a bupivacaine lozenge as pharyngeal anesthesia and a lidocaine spray before EGD was assessed by Salale and coworkers [35]. Ninety-nine adult patients were randomized to receive either a bupivacaine lozenge or lidocaine spray. Patient discomfort and the acceptance of gag reflex during EGD procedures were evaluated. The results showed that patient discomfort and gag reflex during procedure in the bupivacaine lozenge group were significantly lower than the lidocaine spray group. The authors also suggested that bupivacaine lozenge for topical pharyngeal anesthesia before an unsedated EGD procedure verified to be a superior option as compared with lidocaine spray [35].

Chan and colleagues studied the effectiveness of 10% lidocaine pump spray plus plain Strepsils and Strepsils anesthetic lozenge plus distilled water spray for EGD procedure in terms of patient tolerance, taste of anesthetic agent, intensity of numbness, amount of cough or gag, and the degree of discomfort at esophageal intubation. They concluded that topical lidocaine spray was superior to the flavored anesthetic lozenge as a topical pharyngeal anesthesia in unsedated EGD procedure [36]. Furthermore, the safety and efficacy of a lidocaine lollipop as single-agent anesthesia for EGD has been evaluated by Ayoub and coworkers [37]. The main outcome variables of the study were the success rate and safety of local anesthesia by using lidocaine lollipop in addition to the need for intravenous sedation. Their study showed that lidocaine lollipop, a favorable form of pharyngeal anesthesia, was safe and well tolerated for EGD procedure.

5.2. Benzodiazepines

5.2.1. Midazolam

Midazolam is one of the most common drugs used for sedation during GIE procedures. It is a rapid-onset, short duration of action, and water-soluble benzodiazepine with anxiolytic, amnesic, sedative, muscle relaxant, and anticonvulsant properties. These actions are due to the effect of binding to gamma-amino butyric acid receptors in the central nervous system. Midazolam has few adverse effects. Respiratory depression is the most important adverse effect and is synergistic when used in combination with opioids. The standard dose in adult patients is 0.015-0.06 mg/kg [38].

5.3. Opioids

5.3.1. Fentanyl

Fentanyl is a potent synthetic opioid and also commonly used for GIE procedures. It has a rapid onset, short duration of action, and lack of direct myocardial depressant effects. The

onset of action is 30–60 s, and the duration of action is 30–45 min. Generally, the dose for GIE procedure is usually 1–2 mcg/kg, with a maximum dose of 100–150 mcg in adult healthy patients. Because of its analgesic effect, fentanyl is commonly used for therapeutic GIE procedures. Of late, the combination of fentanyl and midazolam is an accepted regimen with a safety profile [39-41]. However, fentanyl can cause respiratory depression including apnea as well as nausea and vomiting. It can reduce the heart rate.

5.3.2. Remifentanil

Remifentanil is a fentanyl analog with a methyl ester group and is hydrolyzed by plasma and tissue esterases. Its metabolism is not affected by genetics, age, hepatic failure, and renal failure. Its action is rapid. The use of remifentanil for sedation in GIE procedures is not entirely recognized. Remifentanil is generally performed by using the continuous infusion technique. The TCI of remifentanil is another preference. The combination of propofol and remifentanil for sedation in GIE procedures is usually used. The study of Abu-Shahwan and Mack demonstrated the efficacy and safety of a combination of propofol and remifentanil for deep sedation in children who underwent GIE procedures [42]. In their study, anesthesia was induced with sevoflurane and nitrous oxide in oxygen, and was maintained with infusion of propofol and remifentanil. All GIE procedures were successfully completed with no complications. However, this combination of propofol and remifentanil demonstrated the reduction of heart rate, blood pressure, and respiratory rate.

Remifentanil in TCI appears to be a satisfactory drug for sedation in GIE procedures. However, propofol in TCI for GIE procedures demonstrates better sedation than remifentanil in TCI. This issue was confirmed by Munoz and colleagues [43]. They compared remifentanil and propofol in TCI for sedation in 69 patients during GIE procedures. The authors concluded that propofol in TCI for sedation in patients who underwent GIE procedures seemed to be an adequate agent. Additionally, propofol in TCI created less adverse effects and higher patient satisfaction than remifentanil in TCI.

5.4. Remimazolam

Remimazolam is a rapidly acting intravenous sedative drug. It combines the properties of midazolam and remifentanil. Additionally, its tendency to cause apnea is very low. Remimazolam has potential to be used as a sedative drug in the intensive care unit and as a novel agent for procedural sedation [44, 45]. Recently, remimazolam was evaluated for sedation in patients who underwent upper GIE procedures by Rogers and McDowell. This clinical trial demonstrated that the time to recovery from sedation of remimazolam was faster and more reliable than midazolam [46]. Moreover, Worthington and colleagues assessed the feasibility of remimazolam for sedation during colonoscopy and reversing the sedative effects of remimazolam with flumazenil in 15 healthy volunteers. The sedation for colonoscopy was successfully completed in more than 70% of subjects. In addition, all subjects rapidly reversed with flumazenil and also rapidly recovered within 10 min. No serious adverse events were observed [47].

http://dx.doi.org/10.5772/60730

5.5. Propofol

Propofol has sedative, hypnotic, and anesthetic properties. However, it does not have analgesic effects. Propofol rapidly crosses the blood–brain barrier. The onset of action is 30–60 s. Dose reduction is needed in patients with cardiac dysfunction and in elderly patients. However, the dose reduction of propofol in patients with moderately severe liver disease or renal failure is not required. Propofol potentiates the effects of analgesic and sedative drugs. The advantage of propofol has been demonstrated for therapeutic GIE procedures and not for diagnostic GIE procedures.

Propofol in combination with opioid or benzodiazepine can cause significant cardiovascular depression and may result in a deeper than expected depth of sedation because of its narrow therapeutic window. Pain at the injection site is the most frequent local complication. Several methods for propofol delivery have been used for GIE procedures. Generally, propofol is administered intravenously as a repeated bolus injection, continuous infusion, or a mixture of both. Currently, the nonanesthesiologist-administered propofol is a controversial issue and also varies among countries.

5.5.1. Propofol for GIE procedures

Generally, propofol is usually used for various GIE procedures. A previous study confirmed that sedation with propofol alone or propofol combined with fentanyl or midazolam in children was safe and effective. However, the use of propofol alone provides lesser sedation and ease of endoscopy than the use of propofol in combination with fentanyl or midazolam [48]. In Siriraj GI Endoscopy Center, the combination of propofol, fentanyl, and/or midazolam was usually used for GIE procedures even in pediatric patients. Moreover, our previous studies also demonstrated the clinical effectiveness of an anesthesiologist-administered sedation outside of the operating room for pediatric GIE procedures. Although, all sedation-related complications were relatively high, all of these complications were transient and easily treated [39, 40, 49, 50]. In terms of procedure-related complications, propofol-based sedation does not increase the rate of colonoscopic perforation [51].

For invasive GIE procedures, propofol-based sedation for ERCP and percutaneous endoscopic gastrostomy procedures in sick and elderly patients by anesthetic personnel with appropriate monitoring was also safe and effective without any serious complications [52-54]. The safety of propofol sedation for EUS with fine needle aspiration procedure was confirmed by Pagano and coworkers [55]. The complication rates for propofol deep sedation and meperidine/midazolam administered for moderate sedation were not significantly different. Furthermore, propofol combined with fentanyl and midazolam is frequently used for GIE procedures including EUS and small bowel enteroscopy [56-60].

5.5.2. Nurse-administered propofol

Several guidelines do not recommend the use of propofol for routine GIE procedures. The safety and efficacy of propofol administered by registered nurses has been reported in a case series including 2000 patients undergoing elective EGD and/or colonoscopy [61]. Another

study demonstrated that trained nurse-administered propofol for GIE sedation in patients with ASA class I, II, and III was safe and effective. The anesthetic support was assisted in 11 patients (0.4%) [62].

5.5.3. Gastroenterologist-administered propofol

Similar to qualified nurses, the gastroenterologist can administer propofol effectively. Several guidelines recommend that gastroenterologist-administered propofol should be used to sedate patients only at mild or moderate sedation levels. Additionally, the patients must have ASA physical status not more than III. The study of Vargo and colleagues confirmed that gastroenterologist-administered propofol for elective ERCP and EUS procedures resulted in the reduction of propofol dosage and the improvement of recovery activity as well as the rapid detection of respiratory depression. This study also demonstrated that gastroenterologist-administered propofol should be a cost-effective sedation technique [63].

5.5.4. Anesthesiologist-administered propofol

Propofol is commonly used by anesthesiologists for anesthesia in GIE procedures. To date, the use of propofol is still controversial. Propofol can be used by well-trained registered nurses or physicians in some countries. However, in developing countries, propofol-based sedation is performed by anesthesiologists or anesthetic nurses. Berzin and coworkers accomplished a cohort study of sedation-related adverse events, patient- and procedure-related risk factors associated with sedation, as well as endoscopist and patient satisfaction with anesthesiologist-administered sedation in 528 patients who underwent ERCP procedures. The study confirmed that anesthesiologist-administered sedation for ERCP patients was safe and effective. Cardiorespiratory-related adverse events were generally minimal [64].

5.6. Fospropofol

Fospropofol is a water-soluble prodrug of propofol that is currently approved for sedation for diagnostic and therapeutic procedures. It is characterized by a smooth and predictable rise and decline rapidly observed following intravenous administration. It does not cause pain on intravenous injection, but it has been associated with paresthesia in the perineal and perianal area. However, fospropofol causes dose-dependent hypotension, respiratory depression, and apnea. Generally, a standard of fospropofol sedation is 6.5 mg/kg. In high-risk and elderly patients, a lower dose should be administered. Bergese and coworkers compared the efficacy and safety of fospropofol in a dose of 4.875 mg/kg and 6.5 mg/kg for sedation in high-risk elderly patients who underwent colonoscopy. This study showed that fospropofol in a dose of 4.875 mg/kg for sedation in high-risk elderly patients who underwent colonoscopy was not a clinically significant advantage. Fospropofol in a dose of 6.5 mg/kg was recommended in the elderly, obese, and high-risk patients when used for moderate sedation [65].

5.7. Ketofol

Ketofol is the combination of ketamine and propofol in various concentrations. It isan agent of choice for a variety of GIE procedures. Ketamine, a neuroleptic anesthetic agent, works on

http://dx.doi.org/10.5772/60730

thalamocortical and limbic N-methyl-D-aspartate receptors. Ketamine stimulates the cardiorespiratory system. A direct effect increases cardiac output, arterial blood pressure, heart rate, and central venous pressures [66]. In contrast, propofol has antiemetic, anxiolytic, hypnotic, and anesthetic properties. Additionally, propofol has a short recovery time without an increase of cardiorespiratory side effects. As a result, the combination of these two drugs has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and post-procedural analgesia. The safety and efficacy of ketofol as a sedoanalgesic agent are dependent on the dose and the ratio of the mixture [67].

Ketofol is also commonly used for sedation during GIE procedures. My previous study evaluated the clinical efficacy of the ketofol and propofol alone when each regimen is used as sedative agents for colonoscopic procedure. A 194 patients were randomized into two groups; 97 patients in group PK received propofol and ketamine and 97 patients in group P received propofol and normal saline for sedation. All patients were premedicated with 0.02–0.03 mg/kg of midazolam. All colonoscopic procedures were completely successful. There were no significant differences in patient tolerance, hemodynamic parameters, recovery activity, patient and endoscopist satisfaction, as well as the sedation-related adverse events between the two groups. In addition, these adverse events were transient and mild in degree [68].

5.8. Dexmedetomidine

Dexmedetomidine is a specific central alpha-2 adrenoreceptor agonist with sedative and analgesic properties. Dexmedetomidine has no effect at the GABA receptor, and is not associated with significant respiratory depression. The patients can be sedated but are able to be awakened to full consciousness easily. It induces a biphasic blood pressure response: high doses cause hypertension, and lower doses cause hypotension and bradycardia. The other disadvantages of dexmedetomidine include a slow onset and longer duration of action [42].

To date, the role of dexmedetomidine for GIE procedures is not entirely established and remains a controversial issue. Samson and colleagues compared the sedation efficacy and the hemodynamic effects of dexmedetomidine, midazolam, and propofol in 90 patients with ASA physical status I or II, who underwent elective diagnostic upper GIE procedures. The results demonstrated that endoscopist satisfaction level, recovery, and the hemodynamic stability in the dexmedetomidine group were significantly better than in the midazolam and the propofol groups [69]. However, dexmedetomidine alone is less effective than the combination of propofol and fentanyl for moderate sedation during ERCP procedure [70]. Most of the patients needed supplementary analgesic and sedative drugs to accomplish the depth of sedation level. However, these findings do not allow us to conclude that propofol alone is better than dexmedetomidine alone, because the conclusion was established for propofol combined with fentanyl. Moreover, dexmedetomidine was associated with higher hemodynamic instability and a prolonged recovery phase [70].

5.9. Ketodex

Ketamine is a dissociative anesthetic agent and works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors. Its actions are described by catalepsy in which eyes remain

open and there is slow nystagmic gaze while corneal and light reflexes remain intact. Direct effects increase cardiac output, blood pressure, heart rate as well as pulmonary arterial and central venous pressures, which stimulates the cardiorespiratory system. However, ketamine produces unpleasant psychological effects including hallucinations, nightmares, and emergence reactions. Dexmedetomidine is a specific central alpha-2 adrenergic agonist that decreases central presynaptic catecholamine release. It has no effect at the GABA receptor, and is not associated with significant respiratory depression. Its properties of sedation, anxiolysis, and analgesia together with its beneficial pharmacokinetics make it a valuable adjunct for procedural and intensive care sedation [66].

The use of ketodex for GIE procedures was reported by Goyal and colleagues [71]. They used a bolus dose of ketamine 2 mg/kg and dexmedetomidine 1 mcg/kg for upper GIE procedures in pediatric patients. The results of the study showed that blood pressure, heart rate, and oxygen saturation did not change significantly from the baseline. The airway interventions were not used. In addition, there were also no laryngospasm and postprocedural shivering. The delirium score was lower than 4 in all patients except for two cases. This case series supported the use of ketodex was safe and clinically effective for upper GIE procedure in pediatric patients [71].

5.10. Muscle relaxants

5.10.1. Cisatracurium

Cisatracurium, an isomer of atracurium, is about three times more potent than atracurium and less tendency to release histamine than atracurium. It experiences spontaneous degradation at physiological pH and temperature by Hofmann elimination. Liver disease does not appear to have an effect on cisatracurium. Pharmacokinetics and pharmacodynamics of cisatracurium in normal adult and liver transplant patients do not show clinically significant differences in the recovery profiles [72]. Because of its beneficial properties, cisatracurium is a muscle relaxant drug of choice for tracheal intubation and maintenance during general anesthesia in GIE procedures [50, 59].

5.10.2. Rocuronium

Rocuronium is a steroidal nondepolarizing neuromuscular blocking drug and has a rapid onset of action. It is a muscle relaxant drug of choice for tracheal intubation and maintenance during general anesthesia in GIE procedures [50, 59, 73]. Rocuronium has emerged as an alternative to succinylcholine for facilitating rapid tracheal intubation in full stomach patients. It is predominantly useful as a relaxant agent for tracheal intubation in patients at risk of hyperkalemia and patients with known or suspected increased intracranial or intraocular pressure. However, rocuronium may be used cautiously in patients with impaired liver function [74].

http://dx.doi.org/10.5772/60730

5.11. Reversal drugs

5.11.1. Naloxone

Naloxone is a pure mu-opioid antagonist with a high affinity for the receptor. It can reverse both the analgesic and respiratory effects of opioids [4, 42]. The standard dosage of intravenous naloxone is 1–2 mcg/kg with a maximum dose of 0.1 mg/kg and up to 2 mg. However, naloxone has a short duration of action and one dose typically only lasts for 30–45 min. Patients should be monitored for at least 2 h after the last dose of naloxone. The adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema, and cardiac dysrhythmias.

5.11.2. Flumazenil

Flumazenil is a benzodiazepine antagonist. It is a highly specific benzodiazepine receptor antagonist and can safely reverse the sedative and respiratory effects caused by benzodiazepines. The adult dose is 0.01 mg/kg and up to 1 mg. Its duration of action is just about 1 h. However, this effect is reversible. Importantly, the patients should be observed for at least 2 h after the administration of flumazenil [4, 42]. The adverse reactions of flumazenil consist of sweating, flushing, nausea/vomiting, hiccup, agitation, abnormal vision, paresthesia, and seizure.

5.12. Sugammadex

Sugammadex is a selective relaxant binding drug that quickly reverses the effects of aminosteroid neuromuscular blocking agents such as rocuronium and vecuronium. It was successfully used to reverse rocuronium-induced neuromuscular block in patients where neostigmine was insufficient. Dogan and colleagues investigated the efficacy of sugammadex after unsatisfactory decurarization following neostigmine administration. This study was performed on 14 patients who experienced inadequate decurarization (TOF < 0.9) with neostigmine after general anesthesia. A dose of 2 mg/kg of sugammadex was used. The result confirmed that sugammadex was successfully performed to reverse rocuronium-induced neuromuscular block in patients where neostigmine was insufficient [75]. The capability to reverse a rocuronium-induced neuromuscular block at any stage and possibly to improve patients' safety might make sugammadex a very attractive drug for the use in day-case anesthesia.

Another study compared the efficacy of sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in elective surgical patients [76]. All patients, ASA physical status I-III obtained a dose of 0.1 mg/kg vecuronium for tracheal intubation and maintenance dose of 0.02–0.03 mg/kg if needed. Neuromuscular blockade was monitored by using acceleromyography. At the end of surgery, patients were randomized to receive either sugammadex 2 mg/kg or neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg. The study showed that mean recovery times to a TOF ratio of 0.8 and 0.7 in the sugammadex group were significantly shorter than in the neostigmine group. No serious adverse events were noted.

The authors concluded that sugammadex presented significantly quicker reversal of vecuronium-induced neuromuscular blockade compared with neostigmine [76].

5.13. Inhalation agents

5.13.1. Sevoflurane

Sevoflurane is an inhalation agent with ideal properties for deep sedation during GIE procedures in pediatric patients. In addition, it is commonly used for balanced general anesthesia. A retrospective study reviewed data from children receiving sevoflurane inhalation administered by an anesthesiologist via laryngeal insufflation to attain deep sedation for outpatient GIE procedures. All patients were adequately sedated with sevoflurane, and no intravenous line was needed. Time to awakening, discharge, and complication rate in the sevoflurane group were significantly lower than in the combination of midazolam, fentanyl, and ketamine, as well as in the propofol alone groups. This report suggested that deep sedation with sevoflurane insufflation for pediatric outpatient GIE procedure is as safe as conventional sedation techniques [77].

Consequently, Meretoja and colleagues compared anesthesia with sevoflurane or halothane for bronchoscopy or gastroscopy, or both in 120 infants and children. All pediatric patients were assigned to receive either 7% sevoflurane or 3% halothane in 66% nitrous oxide in oxygen for induction of anesthesia. Induction time and psychomotor recovery as well as the incidence of nausea/vomiting and cardiac arrhythmia in the sevoflurane group were significantly lower than in the halothane group. This study confirmed that the use of sevoflurane was better than the use of halothane for bronchoscopy and gastroscopy procedures in pediatric patients [78].

5.13.2. Desflurane

Desflurane is an ether inhalational anesthetic agent. It offers the advantage of precise control over depth of anesthesia along with a rapid, predictable, and clear-headed recovery with minimal postoperative adverse events. It also has advantages when used in extremes of age and in obese patients. Desflurane is generally used for the maintenance of balanced general anesthesia because of its rapid recovery. Currently, the use of desflurane may increase the direct costs of anesthetic care [79]. However, no significant differences were demonstrated between desflurane and sevoflurane in the late recovery period.

6. Post-anesthesia care

Blood pressure, heart rate, respiratory rate, oxygen saturation, and level of consciousness are monitored and documented at least every 15 min or less, for a minimum of 30 min after the last dose of sedation drug. These parameters should be monitored and noted in the recovery period. Moreover, the patients should be monitored for at least 2 h after the last dose of a reversal drug. All patients will be discharged from the recovery room once the discharge criteria are completed. Generally, the majority of sedated patients would complete an acceptable score on or before 1 h after GIE procedure. Most delays after satisfactory scores were due

http://dx.doi.org/10.5772/60730

to nonmedical causes [80]. In ambulatory cases, the presence of an escort must be confirmed, and the patients should not drive for at least 24 h.

7. Conclusion

GIE procedure requires some forms of anesthesia. To date, sedation for GIE procedure can be effectively and safely performed by anesthesiologist or nonanesthetic personnel with appropriate patient selection and monitoring. The new anesthetic drugs and monitoring equipments for safety and efficacy are available. However, pre-anesthetic evaluation and preparation, anesthetic drugs used, monitoring practices and post-anesthesia management are still essential for the anesthesia innovations in GIE procedures.

Author details

Somchai Amornyotin

Address all correspondence to: somchai.amo@mahidol.ac.th

Department of Anesthesiology and Siriraj GI Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

References

[1] American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; 96: 1004-17

[2] Cote CJ, Wilson S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* 2006; 118: 2587-602

[3] Muller M, Wehrmann T. How best to approach endoscopic sedation? *Nat Rev Gastroenterol Hepatol* 2011; 8: 481-90

[4] Amornyotin S. Sedation and monitoring for gastrointestinal endoscopy. *World J Gastrointest Endosc* 2013; 5: 47-55

[5] Cacho G, Perez-Calle JL, Barbado A, et al. Capnography is superior to pulse oximetry for the detection of respiratory depression during colonoscopy. *Rev Esp Enferm Dig* 2010; 102: 86-9

[6] Cohen LB. Patient monitoring during gastrointestinal endoscopy: why, when, and how? *Gastrointest Endosc Clin N Am* 2008; 18: 651-63

[7] Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008; 68: 815-26

[8] Amornyotin S. Monitoring for depth of anesthesia: a review. *J Biomed Graph Comput* 2012; 2: 119-27

[9] Bower AL, Ripepi A, Dilger J, et al. Bispectral index monitoring of sedation during endoscopy. *Gastrointest Endosc* 2000; 52: 192-6

[10] Al-Sammak Z, Al-Falaki MM, Gamal HM. Predictor of sedation during endoscopic retrograde cholangiopancreatography-bispectral index vs clinical assessment. *Middle East J Anesthesiol* 2005; 18: 141-8

[11] Paspatis GA, Chainaki I, Manolaraki MM, et al. Efficacy of bispectral index monitoring as an adjunct to propofol deep sedation for ERCP: a randomized controlled trial. *Endoscopy* 2009; 41: 1046-51

[12] Chen SC, Rex DK. An initial investigation of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy. *Am J Gastroenterol* 2004; 99: 1081-6

[13] Drake LM, Chen SC, Rex DK. Efficacy of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy: a randomized controlled trial. *Am J Gastroenterol* 2006; 101: 2003-7

[14] Qadeer MA, Vargo JJ, Patel S, et al. Bispectral index monitoring of conscious sedation with the combination of meperidine and midazolam during endoscopy. *Clin Gastroenterol Hepatol* 2008; 6: 102-8

[15] Kreuer S, Biedler A, Larsen R, Altmann S, Wilhelm W. Narcotrend monitoring allows faster emergence and a reduction of drug consumption in propofol-remifentanil anesthesia. *Anesthesiology* 2003; 99: 34-41

[16] Wehmann T, Grotkamp J, Stergiou N, et al. Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized, controlled trial. *Gastrointest Endosc* 2002; 56: 817-24

[17] Amornyotin S, Srikureja W, Chalayonnawin W, Kongphlay S. Dose requirement and complication of diluted and undiluted propofol for deep sedation for endoscopic retrograde cholangiopancreatography. *Hepatobiliary Pancreat Dis Int* 2011; 10: 313-8

[18] Amornyotin S, Chalayonnawin W, Kongphlay S. Deep sedation for endoscopic retrograde cholangiopancreatography: a comparison between clinical assessment and Narcotrend™ monitoring. *Med Devices* (Auckl) 2011; 4: 43-9

[19] Amornyotin S, Srikureja W, Chalayonnavin W, Kongphlay S, Chatchawankitkul S. Topical viscous lidocaine solution versus lidocaine spray for pharyngeal anesthesia in unsedated esophagogastroduodenoscopy. *Endoscopy* 2009; 41: 581-6

[20] Soweid AM, Yaghi SR, Jamali FR, et al. Posterior lingual lidocaine: a novel method to improve tolerance in upper gastrointestinal endoscopy. *World J Gastroenterol* 2011; 17: 5191-6

[21] Ramirez MO, Segovia BL, Cuevas MAG, et al. Glossopharyngeal nerve block versus lidocaine spray to improve tolerance in upper gastrointestinal endoscopy. *Gastroenterol Res Pract* 2013; Article ID 264509, 4 pages, http://dx.doi.org/10.1155/2013/264509

[22] Guarracino F, Lapolla F, Cariello C, et al. Target controlled infusion: TCI. *Minerva Anestesiol* 2005; 71: 335-7

[23] Mazanikov M, Udd M, Kylanpaa L, et al. A randomized comparison of target-controlled propofol infusion and patient-controlled sedation during ERCP. *Endoscopy* 2013; 45: 915-9

[24] Mazanikov M, Udd M, Kylanpaa L, et al. Patient-controlled sedation with propofol and remifentanil for ERCP: a randomized, controlled study. *Gastrointest Endosc* 2011; 73: 260-6

[25] Mandel JE, Tanner JW, Lichtenstein GR, et al. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanil versus midazolam/fentanyl for colonoscopy. *Anesth Analg* 2008; 106: 434-9

[26] Mazanikov M, Udd M, Kylanpaa L, et al. Dexmedetomidine impairs success of patient-controlled sedation in alcoholics during ERCP: a randomized, double-blind, placebo-controlled study. *Surg Endosc* 2013; 27: 2163-8

[27] O'Connor JPA, O'Morain CA, Vargo JJ. Computer-assisted propofol administration. *Digestion* 2010; 82: 124-6

[28] Pambianco DJ, Vargo JJ, Pruitt RE, Hardi R, Martin JF. Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study. *Gastrointest Endosc* 2011; 73: 765-72

[29] Pambianco DJ, Whitten CJ, Moerman A, Struys MM, Martin JF. An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. *Gastrointest Endosc* 2008; 68: 542-7

[30] Hemmerling TM. Automated anesthesia. *Curr Opin Anesthesiol* 2009; 22: 757-63

[31] Hemmerling TM, Terrasini N. Robotic anesthesia: not the realm of science fiction any more. *Curr Opin Anesthesiol* 2012; 25:736-42

[32] Applegate II RL, Gildea B, Patchin R, et al. Telemedicine pre-anesthesia evaluation: a randomized pilot trial. Telemed e-Health 2013; 19: 211-6

[33] Mogensen S, Treldal C, Feldager E, et al. New lidocaine lozenge as topical anesthesia compared to lidocaine viscous oral solution before upper gastrointestinal endoscopy. *Local Reg Anesth* 2012; 5: 17-22

[34] Tumminakatte ZU, Nagaraj P. Double blinded randomized controlled trial comparing lidocaine viscous and lidocaine lozenges prior to upper gastrointestinal endoscopy. *Indian J Public Health Res Develop* 2013; 4: 256-60

[35] Salale N, Treldal C, Mogensen S, et al. Bupivacaine lozenge compared with lidocaine spray as topical pharyngeal anesthetic before unsedated upper gastrointestinal endoscopy: a randomized, controlled trial. *Clin Med Insights: Gastroenterol* 2014; 7: 55-9

[36] Chan CKO, Fok KL, Poon CM. Flavored anesthetic lozenge versus Xylocaine spray used as topical pharyngeal anesthesia for unsedated esophagogastroduodenoscopy: a randomized placebo-controlled trial. *Surg Endosc* 2010; 24: 897-901

[37] Ayoub C, Skoury A, Abdul-Baki H, et al. Lidocaine lollipop as single-agent anesthesia in upper GI endoscopy. *Gastrointest Endosc* 2007; 66: 786-93

[38] Hausman LM, Reich DL. Providing safe sedation/analgesia: an anesthesiologist's perspective. *Gastrointest Endosc Clin N Am* 2008; 18: 707-16

[39] Amornyotin S, Srikureja W, Pausawasdi N, Prakanrattana U, Kachintorn U. Intravenous sedation for gastrointestinal endoscopy in very elderly patients of Thailand. *Asian Biomed* 2011; 5: 485-91

[40] Amornyotin S, Aanpreung P, Prakarnrattana U, et al. Experience of intravenous sedation for pediatric gastrointestinal endoscopy in a large tertiary referral center in a developing country. *Pediatr Anesth* 2009; 19: 784-91

[41] Amornyotin S, Prakanrattana U, Chalayonnavin W, Kongphlay S. Intravenous sedation for endoscopic ultrasonography in Siriraj Hospital. *Thai J Anesthesiol* 2009; 35: 181-90

[42] Amornyotin S. Sedative and analgesic drugs for gastrointestinal endoscopic procedure. *J Gastroenterol Hepatol Res* 2014; 3: 1133-44

[43] Abu-Shahwan I, Mack D. Propofol and remifentanil for deep sedation in children undergoing gastrointestinal endoscopy. *Pediatr Anesth* 2007; 17: 460-3

[44] Munoz L, Arevalo JJ, Reyesc LE, et al. Remifentanil vs. propofol controlled infusion for sedation of patients undergoing gastrointestinal endoscopic procedures: a clinical randomized controlled clinical trial. *Rev Colomb Anestesiol* 2013; 41: 114-9

[45] Goudra BG, Singh PM. Remimazolam: the future of its sedative potential. *Saudi J Anesth* 2014; 8: 388-91

[46] Rogers WK, McDowell TS. Remimazolam, a short-acting GABA (A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. *IDrugs* 2010; 13: 929-37

[47] Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg* 2013; 117: 1093-100

[48] Disma N, Astuto M, Rizzo G, et al. Propofol sedation with fentanyl or midazolam during esophagogastroduodenoscopy in children. *Eur J Anesthesiol* 2005; 22: 848-52

[49] Amornyotin S, Aanpreung P. Clinical effectiveness of an anesthesiologist-administered intravenous sedation outside of the main operating room for pediatric upper gastrointestinal endoscopy in Thailand. *Int J Pediatr* 2010; 2010 [DOI: 10.1155/2010/748564]

[50] Amornyotin S, Prakanrattana U, Chalayonnavin W, Kongphlay S, Chantakard S. Anesthesia for pediatric gastrointestinal endoscopy in a tertiary care teaching hospital. *Thai J Anesthesiol* 2008; 34: 265-72

[51] Amornyotin S, Prakanrattana U, Kachintorn U, Chalayonnavin W, Kongphlay S. Propofol-based sedation does not increase rate of perforation during colonoscopic procedure. *Gastroenterol Insights* 2010; 2: e4

[52] Amornyotin S, Kachintorn U, Chalayonnawin W, Kongphlay S. Propofol-based deep sedation for endoscopic retrograde cholangiopancreatography procedure in sick elderly patients in a developing country. *Ther Clin Risk Manage* 2011; 7: 251-5

[53] Amornyotin S, Prakanrattana U, Chalayonnavin W, Kongphlay S, Kongmueng B. Anesthesia for percutaneous endoscopic gastrostomy in Siriraj Hospital. *Thai J Anesthesiol* 2009; 35: 39-47

[54] Amornyotin S, Chalayonnavin W, Kongphlay S. Propofol-based sedation does not increase rate of complication during percutaneous endoscopic gastrostomy procedure. *Gastroenterol Res Pract* 2011; 2011 [DOI: 10.1155/2011/134819]

[55] Pagano N, Arosio M, Romeo F, et al. Balanced propofol sedation in patients undergoing EUS-FNA: a pilot study to assess feasibility and safety. *Diagn Ther Endosc* 2011; 2011: 542159

[56] Amornyotin S. Sedation for colonoscopy in children. *J Gastroenterol Hepatol Res* 2013; 2: 555-60

[57] Amornyotin S, Songarj P, Kongphlay S. Deep sedation with propofol and pethidine versus moderate sedation with midazolam and fentanyl in colonoscopic procedure. *J Gastroenterol Hepatol Res* 2013; 2: 885-90

[58] Amornyotin S, Kongphlay S. Esophagogastroduodenoscopy procedure in sick pediatric patients: a comparison between deep sedation and general anesthesia technique. *J Anesth Clin Res* 2012; 3: 1000185

[59] Amornyotin S, Kachintorn U, Kongphlay S. Anesthetic management for small bowel enteroscopy in a World Gastroenterology Organizing Endoscopy Training Center. *World J Gastrointest Endosc* 2012; 4: 189-93

[60] Amornyotin S, Kongphlay S. Anesthetic trainee-administered propofol deep sedation for small bowel enteroscopy procedure in elderly patients. *J Gastroenterol Hepatol Res* 2014; 3: 1117-29

[61] Rex DK, Overley C, Kinser K, et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am J Gastroenterol* 2002; 97: 1159-63

[62] Slagelse C, Vilmann P, Hornslet P, Hammering A, Mantoni T. Nurse-administered propofol sedation for gastrointestinal endoscopic procedures: first Nordic results from implementation of a structured training program. Scand J Gastroenterol 2011; 46: 1503-9

[63] Vargo JJ, Zuccaro G, Dumot JA, et al. Gastroenterologist administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology* 2002; 123: 8-16

[64] Berzin TM, Sanaka S, Barnett SR, et al. A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. *Gastrointest Endosc* 2011; 73: 710-7

[65] Bergese SD, Dalal P, Vandse R, et al. A double-blind, randomized, multicenter, dose-ranging study to evaluate the safety and efficacy of fospropofol disodium as an intravenous sedative for colonoscopy in high-risk populations. *Am J Ther* 2013; 20: 163-71

[66] Amornyotin S. Ketamine: pharmacology revisited. *Int J Anesthesiol Res* 2014; 2: 42-4 [DOI: 10.14205/2310-9394.2014.02.02.4]

[67] Amornyotin S. Ketofol: a combination of ketamine and propofol. *J Anesth Crit Care Open Access* 2014; 1: 00031 [DOI:10.15406/jaccoa.2014.01.00031]

[68] Amornyotin S, Chalayonnawin W, Kongphlay S. Clinical efficacy of the combination of propofol and ketamine (ketofol) for deep sedation for colonoscopy. Gut 2012; 61 (Suppl 2): A339-40

[69] Samson S, George SK, Vinoth B, Khan MS, Akila B. Comparison of dexmedetomidine, midazolam, and propofol as an optimal sedative for upper gastrointestinal endoscopy: a randomized controlled trial. *J Dig Endosc* 2014; 5: 51-7

[70] Muller S, Borowics SM, Fortis EAF, et al. Clinical efficacy of dexmedetomidine alone is less than propofol for conscious sedation during ERCP. *Gastrointest Endosc* 2008; 67: 651-9

[71] Goyal R, Singh S, Shukla RN, Patra AK, Bhargava DV. Ketodex, a combination of dexmedetomidine and ketamine for upper gastrointestinal endoscopy in children: a preliminary report. *J Anesth* 2013; 27: 461-3

[72] De Wolf AM, Freeman JA, Scott VL, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anesth* 1996; 76: 624-8

[73] Amornyotin S, Pranootnarabhal T, Chalayonnavin W, Kongphlay S. Anesthesia for gastrointestinal endoscopy from 2005-2006 in Siriraj Hospital: a prospective study. *Thai J Anesthesiol* 2007; 33: 93-101

[74] Magorian T, Wood P, Caldwell J, et al. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg* 1995; 80: 754-9

[75] Dogan E, Akdemir MS, Guzel A, et al. A miracle that accelerates operating room functionality: sugammadex. *Bio Med Res Int* 2014 (2014), Article ID 945310, 4 pages [10.1155/2014/945310]

[76] Khuenl-Brady K, Wattwil M, Vanacker BF, et al. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. *Anesth Analg* 2010; 110: 64-73

[77] Montes RG, Bohn RA. Deep sedation with inhaled sevoflurane for pediatric outpatient gastrointestinal endoscopy. *J Pediatr Gastroenterol Nutr* 2000; 31: 41-6

[78] Meretoja OA, Taivainen T, Raiha L, Korpela R, Wirtavuori K. Sevoflurane-nitrous oxide or halothane-nitrous oxide for pediatric bronchoscopy and gastroscopy. *Br J Anesth* 1996; 76: 767-71

[79] Kapoor MC, Vakamudi M. Desflurane-revisited. *J Anesthesiol Clin Pharmacol* 2012; 28: 92-100

[80] Amornyotin S, Chalayonnavin W, Kongphlay S. Recovery pattern and home-readiness after ambulatory gastrointestinal endoscopy. J Med Assoc Thai 2007; 90: 2352-8

Chapter 3

Fine-Needle Aspirates v2.0 — The Molecular Era

Louis Buscail and Pierre Cordelier

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60542

Abstract

Tissue biopsies are required for diagnosis, prognosis, and to measure individual drug response markers for patient management. For pancreatic adenocarcinoma, surgically harvested tissues are often used to collect data and perform genomic analysis to identify driver oncogenes and specific mutations, or to quantify a handpick of (micro)RNAs and proteins biomarkers. However, such strategy raises many concerns not only because 80% of patients diagnosed with pancreatic adenocarcinoma are not eligible for surgery, meaning that biopsies are not collected, but also because repeated core biopsies are related to higher risk of morbidity, are expensive and logistics can be limiting. Alternative sample collection methods include fine-needle aspirates (FNA) collected under endoscopic ultrasound (EUS). In this chapter, we will describe how EUS-FNA material can be a wealthy source of biomarkers for pancreatic cancer patient management. In greater details, we will review how DNA, micro(RNA), or protein analysis can help stratify pancreatic adenocarcinoma patients, from single events analysis, to cutting-edge, high-throughput studies.

Keywords: FNA, microbiopsies, pancreatic diseases, NGS, miRNA, digital PCR

1. Introduction

Tissue biopsies are required for diagnosis, prognosis, and to measure individual drug response markers for patient management. For pancreatic adenocarcinoma, surgically harvested tissues are often used to collect data and perform genomic analysis to identify driver oncogenes and specific mutations, or to quantify a handpick of (micro)RNAs and proteins biomarkers. However, such strategy raises many concerns not only because 80% of patients diagnosed with

pancreatic adenocarcinoma are not eligible for surgery, meaning that biopsies are not collected, but also because repeated core biopsies are related to higher risk of morbidity, are expensive and logistics can be limiting. Alternative sample collection methods include fine-needle aspirates (FNA) collected under endoscopic ultrasound (EUS). In this chapter, we will describe how EUS-FNA material can be a wealthy source of biomarkers for pancreatic cancer patient management. In greater details, we will review how DNA, micro(RNA), or protein analysis can help stratify pancreatic adenocarcinoma patients, from single events analysis, to cutting-edge, high-throughput studies.

2. Fine-needle aspirates for pancreatic cancer diagnosis and prognosis

Pancreatic cancer remains one of the most deadly types of tumor. The five-year survival rate after diagnosis is less than 3.5% [1]. Only 15% of pancreatic ductal adenocarcinoma (pancreatic cancer) patients can be diagnosed at a resectable and possible curative stage. The remaining patients diagnosed with locally advanced and/or metastatic tumors are treated in a palliative way. Single-agent gemcitabine, although not dramatically improving survival, has demonstrated a significant clinical benefit and has become the standard chemotherapy for advanced pancreatic cancer [2]. Recently, FOLFIRINOX protocol and association gemcitabine-Nab-paclitaxel regimens were found to improve the survival of metastatic patients when compared to gemcitabine alone [3, 4]. However, median survival does not exceed six and ten months for metastatic and locally advanced pancreatic cancer, respectively [5]. One way to improve pancreatic cancer management is to establish a rapid and clear diagnosis in order to operate or to start a medical treatment as soon as possible. One of the critical clinical conditions is the differentiation of pancreatic cancer from focal pancreatitis. It is indeed necessary to avoid unnecessary resection of benign lesions (such chronic pancreatitis in its pseudotumoral form or autoimmune pancreatitis) or to delay the treatment of pancreatic cancer in a subset of patients. Recent advances in abdominal imaging techniques may favor a more rapid histological diagnosis and also may resolve some of these problems of differential diagnosis. Among these imaging techniques, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a rapid, safe, cost-effective, and accurate technique for evaluating and staging pancreatic tumors [6–8]. EUS allows to guide FNA of solid pancreatic lesions for cytopathological analysis. However, its performance for the diagnosis of malignancy varies widely with a sensitivity ranging from 75–94% and an accuracy of 78–95%. In addition, if the specificity approaches 100%, its negative predictive value ranges from 40–75%. In addition, EUS-FNA may be inconclusive in up to 20% of cases [8, 9]. Overall, false-negative rates and atypical or suspicious diagnoses remain relatively frequent using cytopathological analysis [9]. The improvement of molecular biology techniques, including DNA and RNA amplification, permits the analysis and quantification of molecular markers in cytological samples. In addition, EUS-FNA is the main clinical appliance for cytological and histological material collection from locally advanced pancreatic cancer that represents 85% of pancreatic cancer patients. This chapter depicts the widespread potential for the molecular analysis of samples obtained by EUS-FNA in conducting translational studies to improve knowledge and diagnosis of pancreatic cancer.

http://dx.doi.org/10.5772/60542

3. Identification of key mutations in tumor suppressor genes and oncogenes using FNA material

We and others have demonstrated that DNA extracted from EUS-FNA material may permit to detect single DNA mutations in key tumor suppressor genes and oncogenes for better pancreatic cancer patients management (for review [6]). The next challenge is to identify new technologies that are more sensitive than standard quantitative PCR (qPCR) or that may allow screening of multiple mutations in a few nanograms of DNA. Recently, digital PCR (dPCR) has shown promise in cancer diagnosis, although current dPCR systems have lower throughput than qPCR systems. dPCR is based on absolute nucleic acid quantification following partitioning of individual molecules into multiple replicate reactions at limiting dilution. Following reaction, the starting concentration of template is determined by Poisson statistical analysis of the number of positive (with amplified target) and negative (without amplified target) detected reactions [10]. By essence, dPCR is anticipated to be more tolerant to PCR inhibitors by virtue of being an end-point approach; with improved amplification efficiency and, thus, sensitivity. Accordingly, Hindson et al. recently compared the performance of dPCR to real-time PCR in clinical specimens. When applied to serum microRNA biomarker analysis, dPCR was proved to provide superior diagnostic performance for identifying individuals with cancer than qPCR [10]. Similar results have been reported in a small cohort of patients with pancreatic cancer. Dr Capella's group recently demonstrated that digital PCR provides a robust and quantitative assay for KRAS mutant alleles detection in routinely obtained samples [11]. The next objective is to transfer this approach to the screening of DNA mutations in material from EUS-FNA.

Large pancreatic cancer sequencing initiatives are revealing a vast array of molecular aberrations in histologically indistinguishable tumors (for review [12]). Of importance, the mutational burden seems to be particularly heterogeneous and this has major implications in therapeutic development and clinical care. Indeed, better understanding the genetic and molecular basis of cancer may not only help to stratify patients but also develop new classes of therapies that selectively target molecular mechanisms that are essential for the survival and proliferation of cancer cells. Unfortunately, such analysis requires amounts of material that are out of reach following EUS-FNA. Alternatively, targeted next-generation sequencing (NGS) can be performed with minimal amount of DNA. One of these approaches is based on the Ion Torrent Ampliseq technology. In thyroid cancer, 5–10 ng of input DNA is sufficient for the successful analysis of virtually all samples, either thyroid tissue or fine-needle aspiration samples, and revealed point mutations in specific types of thyroid cancer [13]. We recently translated this method to the analysis of FNA material from pancreatic tumors; we found that this approach is feasible with minimal amount of DNA. Using the comprehensive cancer panel, we verified KRAS mutation and discovered new mutations in key oncogenic drivers and tumor suppressor genes that are currently validated by qPCR. Thus, targeted NGS holds great promise for pancreatic cancer patient stratification and management.

4. Quantification of microRNA in FNA material

Beside DNA, microRNAs are well-characterized biomarkers for pancreatic cancer management (for review [14]). To date, most studies are limited to the quantification of a handful of selected candidate microRNAs in EUS-FNA material. For example, Dr Szafranska's group recently validated a 5-miRNA expression classifier to improve preoperative detection of pancreatic cancer [15]. While these results are encouraging, further developments are needed to analyze simultaneously several dozens of microRNA in EUS-FNA material. Current methods for the detection and measurement of microRNA expression include the abovementioned standard quantitative PCR and microarray based analysis. However, these methods suffer several limitations when used in large clinical studies where a high-throughput and highly quantitative technology is needed for the efficient characterization of a large number of microRNA transcripts in clinical samples. Recently, high-throughput qPCR-based microfluidic technology (Biomark Fluidigm) has been evaluated to quantify microRNA expression in lung cancer [16]. The authors demonstrate that (1) the technic is highly reproducible, (2) multiplex results correlate closely with singleplex qPCR, (3) throughput is 5–20 times higher, and (4) cost is approximately 50–100 times lower than conventional assays [16]. We recently benchmarked and validated this approach for the analysis of 96 candidate microRNAs in EUS-FNA material from pancreatic cancer patients, starting from 200 ng of total RNA (Fig. 1). In addition, we found that amplification quality was greater when using material collected from FNA and conserved in RNA later, as compared to material extracted from archived slides (personal observation).

While the measurement of microRNA expression in rare cell populations or in precious samples such as FNA still poses practical challenges due to the low amount of RNA present, alternative techniques have been developed to quantify the complete microRNA landscape in less than 50 ng of total RNA. Such highly sensitive real-time quantitative PCR strategy utilizes microfluidic array cards containing prespotted TaqMan probes that allows the detection of mature miRNAs in small reaction volumes. This approach, namely OpenArray® MicroRNA Panels, was used for the characterization of microRNA expression in mouse hematopoietic stem cells [17]. We have recently validated this approach for the detection and quantification of circulating microRNA in patients (Buscail *et al.*, Molecular Therapy, in press); similar experiments are currently ongoing to characterize the microRNA pattern of expression in EUS-FNA material from patients with pancreatic cancer.

5. Multiplexed protein analysis in FNA material

EUS-FNA has been proven as a useful method for diagnosing pancreatic lesions and is associated with high accuracy in moderately to poorly differentiated pancreatic cancer. However, diagnosis of well-differentiated cancer or early stage tumors can be challenging; in these situations, an indeterminate diagnosis is often rendered. Ancillary stains can provide much needed supportive evidence. Many studies have used a large number of stains to

http://dx.doi.org/10.5772/60542

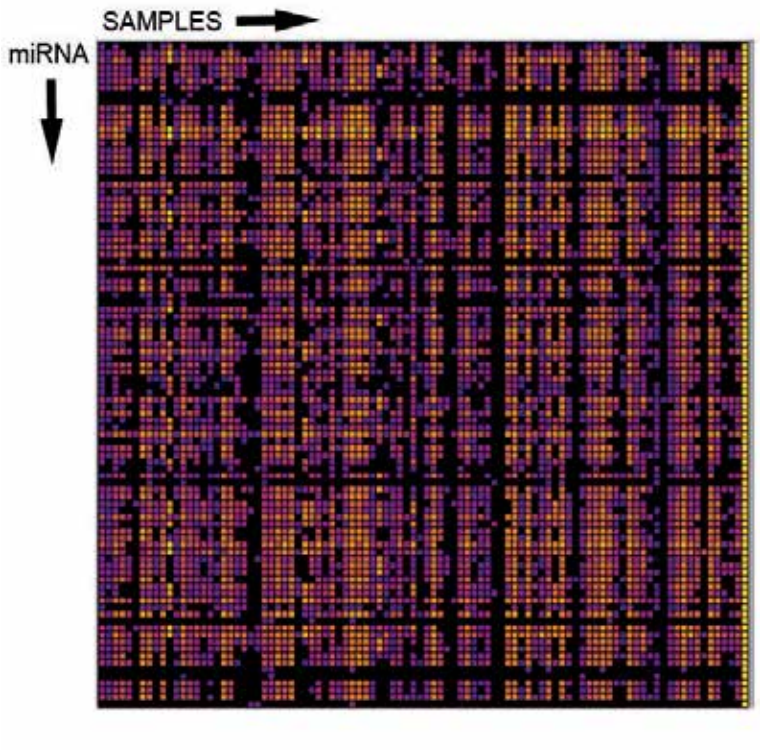

Figure 1. qPCR-based microfluidic analysis of microRNA expression in pancreatic tumors FNA. *Unpublished results*.

document an immunohistochemical profile of pancreatic cancer [18–25], but the number of proteins than can be analyzed is often limiting. Recently, multiplexed flow cytometry and mass cytometry have been proposed to examine an expanded set of markers (up to 50). However, flow cytometry is often limited by the number of markers that can be analyzed due to spectral overlap. Also, mass cytometry requires cells to be vaporized during sample preparation, resulting in sample loss [26]. Very recently, Ullal *et al.* designed a remarkable strategy based on antibody barcoding with photocleavable DNA platform to perform multiplexed protein measurements in small amounts of clinical sample material [27]. This method showed high reproducibility and achieved single-cell sensitivity. Using this strategy, the authors successfully analyzed the expression of 90 candidate proteins and demonstrated that this method could be used to identify pathway responses to molecularly targeted drugs in FNA, to help predict drug response in patients with lung cancer [27]. While technically challenging, it is tempting to speculate that this approach will be soon translated to the analysis of EUS-FNA material from patients with pancreatic cancer.

6. Future development: Defining pancreatic tumors heterogeneity at the cellular level

As stated before, large-scale genomic studies on pancreatic tumors revealed marked inter- and intratumoral heterogeneity and complexity, and may explain the lack of success of conventional, disease-based approaches, therapies. A better understanding of the underlying molecular pathology at the cellular level may undoubtedly lead to novel therapeutics development. Indeed, many biological programs are performed under the assumption that all cells of a particular type are identical. However, recent data suggest that individual cells within a single population may differ quite significantly and these differences can drive the health and function of the entire cell population, including major variation in the tumor cell microenvironment. Single cell analysis comprises a broad field that covers advanced optical, electrochemical, mass spectrometry instrumentation, and sensor technology, as well as separation and sequencing techniques. Although the approaches currently in use can offer snapshots of single cells, the methods are often not amenable to longitudinal studies that monitor changes in individual cells *in situ*. Recently, David Ting *et al.*, from Dr Harber's group in Harvard, have performed epitope-independent microfluidic capture, followed by single-cell RNA sequencing, to analyze circulating pancreatic tumor cells (CTCs) in experiment models [28]. The authors demonstrate that CTCs exhibit a very high expression of stromal-derived extracellular matrix proteins, including SPARC, a tentative prognosis marker for nab-paclitaxel-based therapy. At present, the clinical use of single-cell analysis is – with the exception of preimplantation diagnosis – still in its infancy. However, we are facing an era of integrated single-cell genomic, epigenomic, transcriptomic, and proteomic analysis that will revolutionize whole-organism science. Single-cell diagnostics will be instrumental for the realization of personalized medicine for pancreatic cancer patients and for the development of completely novel therapeutic concepts.

7. Conclusion

At present, the classification of tumors is mainly based on observational characteristics, such as morphology, phenotype, or developmental origin. The current progress in developing sophisticated approaches for investigating EUS-FNA material will definitely improve our understanding of pancreatic cancer at multiple levels, through (1) a better definition of cell types and intercellular variability, (2) a possibility to carry large-scale mutational, transcriptomic, or epigenomic analyses, and (3) an improved identification of rare cell types, to play an increasing role in the detection of minimal residual disease or in the analysis of circulating tumor cells. Accordingly, there are existing opportunities for more rapid improvement in outcomes by adopting a more stratified or personalized approach using markers from different molecular species. However, these progresses will have to complain not only with the development of new drugs but also with clinical care and regulatory agencies. Nonetheless, it is tempting to speculate that EUS-FNA-based molecular evidences will soon drive decision making for patients with advanced pancreatic cancer.

http://dx.doi.org/10.5772/60542

Author details

Louis Buscail[1,2,3] and Pierre Cordelier[1,2*]

*Address all correspondence to: pierre.cordelier@inserm.fr

1 Inserm, UMR1037 CRCT, F-31000 Toulouse, France

2 Université Toulouse III-Paul Sabatier, UMR1037 CRCT, F-31000 Toulouse, France

3 Department of Gastroenterology, CHU Toulouse- Rangueil, Toulouse, France

References

[1] Hidalgo M. Pancreatic cancer. N Engl J Med. 2010 Apr 29;362(17):1605–17.

[2] Ducreux M, Boige V, Malka D. Treatment of advanced pancreatic cancer. Semin Oncol. 2007 Apr;34(2 Suppl 1):S25–30.

[3] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817–25.

[4] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691–703.

[5] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan; 63(1):11–30.

[6] Bournet B, Gayral M, Torrisani J, Selves J, Cordelier P, Buscail L. Role of endoscopic ultrasound in the molecular diagnosis of pancreatic cancer. World J Gastroenterol WJG. 2014 Aug 21;20(31):10758–68.

[7] Kato K, Kamada H, Fujimori T, Aritomo Y, Ono M, Masaki T. Molecular biologic approach to the diagnosis of pancreatic carcinoma using specimens obtained by EUS-guided fine needle aspiration. Gastroenterol Res Pract. 2012;2012:243524.

[8] Yoshinaga S, Suzuki H, Oda I, Saito Y. Role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for diagnosis of solid pancreatic masses. Dig Endosc Off J Jpn Gastroenterol Endosc Soc. 2011 May;23 Suppl 1:29–33.

[9] Bournet B, Migueres I, Delacroix M, Vigouroux D, Bornet J-L, Escourrou J, et al. Early morbidity of endoscopic ultrasound: 13 years' experience at a referral center. Endoscopy. 2006 Apr;38(4):349–54.

[10] Hindson CM, Chevillet JR, Briggs HA, Gallichotte EN, Ruf IK, Hindson BJ, et al. Absolute quantification by droplet digital PCR versus analog real-time PCR. Nat Methods. 2013 Oct;10(10):1003–5.

[11] Azuara D, Ginesta MM, Gausachs M, Rodriguez-Moranta F, Fabregat J, Busquets J, et al. Nanofluidic Digital PCR for KRAS Mutation Detection and Quantification in Gastrointestinal Cancer. Clin Chem. 2012 Sep 1;58(9):1332–41.

[12] Chang DK, Grimmond SM, Biankin AV. Pancreatic cancer genomics. Curr Opin Genet Dev. 2014 Feb;24:74–81.

[13] Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab. 2013 Nov;98(11):E1852–60.

[14] Gayral M, Jo S, Hanoun N, Vignolle-Vidoni A, Lulka H, Delpu Y, et al. MicroRNAs as emerging biomarkers and therapeutic targets for pancreatic cancer. World J Gastroenterol WJG. 2014 Aug 28;20(32):11199–209.

[15] Brand RE, Adai AT, Centeno BA, Lee LS, Rateb G, Vignesh S, et al. A microRNA-based test improves endoscopic ultrasound-guided cytologic diagnosis of pancreatic cancer. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2014 Oct;12(10):1717–23.

[16] Jang JS, Simon VA, Feddersen RM, Rakhshan F, Schultz DA, Zschunke MA, et al. Quantitative miRNA expression analysis using fluidigm microfluidics dynamic arrays. BMC Genomics. 2011;12:144.

[17] Hu W, Park CY. Measuring microRNA expression in mouse hematopoietic stem cells. Methods Mol Biol Clifton NJ. 2014;1185:121–40.

[18] Dim DC, Jiang F, Qiu Q, Li T, Darwin P, Rodgers WH, et al. The usefulness of S100P, mesothelin, fascin, prostate stem cell antigen, and 14-3-3 sigma in diagnosing pancreatic adenocarcinoma in cytological specimens obtained by endoscopic ultrasound guided fine-needle aspiration. Diagn Cytopathol. 2014 Mar;42(3):193–9.

[19] Hosoda W, Sasaki E, Murakami Y, Yamao K, Shimizu Y, Yatabe Y. BCL10 as a useful marker for pancreatic acinar cell carcinoma, especially using endoscopic ultrasound cytology specimens. Pathol Int. 2013 Mar;63(3):176–82.

[20] Morgan TK, Hardiman K, Corless CL, White SL, Bonnah R, Van de Vrugt H, et al. Human pancreatic cancer fusion 2 (HPC2) 1-B3: a novel monoclonal antibody to screen for pancreatic ductal dysplasia. Cancer Cytopathol. 2013 Jan;121(1):37–46.

[21] Carrara S, Cangi MG, Arcidiacono PG, Perri F, Petrone MC, Mezzi G, et al. Mucin expression pattern in pancreatic diseases: findings from EUS-guided fine-needle aspiration biopsies. Am J Gastroenterol. 2011 Jul;106(7):1359–63.

[22] Fujita H, Ohuchida K, Mizumoto K, Itaba S, Ito T, Nakata K, et al. Gene expression levels as predictive markers of outcome in pancreatic cancer after gemcitabine-based adjuvant chemotherapy. Neoplasia N Y N. 2010 Oct;12(10):807–17.

[23] Awadallah NS, Shroyer KR, Langer DA, Torkko KC, Chen YK, Bentz JS, et al. Detection of B7-H4 and p53 in pancreatic cancer: potential role as a cytological diagnostic adjunct. Pancreas. 2008 Mar;36(2):200–6.

[24] Itoi T, Takei K, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, et al. Immunohistochemical analysis of p53 and MIB-1 in tissue specimens obtained from endoscopic ultrasonography-guided fine needle aspiration biopsy for the diagnosis of solid pancreatic masses. Oncol Rep. 2005 Feb;13(2):229–34.

[25] McCarthy DM, Maitra A, Argani P, Rader AE, Faigel DO, Van Heek NT, et al. Novel markers of pancreatic adenocarcinoma in fine-needle aspiration: mesothelin and prostate stem cell antigen labeling increases accuracy in cytologically borderline cases. Appl Immunohistochem Mol Morphol AIMM Off Publ Soc Appl Immunohistochem. 2003 Sep;11(3):238–43.

[26] Rebours V, Le Faouder J, Laouirem S, Mebarki M, Albuquerque M, Camadro J-M, et al. In situ proteomic analysis by MALDI imaging identifies ubiquitin and thymosin-β4 as markers of malignant intraductal pancreatic mucinous neoplasms. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2014 Apr;14(2):117–24.

[27] Ullal AV, Peterson V, Agasti SS, Tuang S, Juric D, Castro CM, et al. Cancer cell profiling by barcoding allows multiplexed protein analysis in fine-needle aspirates. Sci Transl Med. 2014 Jan 15;6(219):219ra9.

[28] Ting DT, Wittner BS, Ligorio M, Vincent Jordan N, Shah AM, Miyamoto DT, et al. Single-cell RNA sequencing identifies extracellular matrix gene expression by pancreatic circulating tumor cells. Cell Rep. 2014 Sep 25;8(6):1905–18.

Section 2

Gastrointestinal Tract

Chapter 4

Endoscopic Treatment of Gastrointestinal Bleedings

Paul Mitrut, Liliana Streba, Anca Oana Docea,
Adina Kamal, Sorin Ioan Zaharie ,
Nicolae-Dragoș Mărgăritescu and
Costin Teodor Streba

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61192

Abstract

Digestive endoscopy represents an essential diagnostic and curative tool used when presented with a suspicion of gastrointestinal (GI) bleeding. Its role is not only confined to primary detection but also to establishing the severity of a lesion and providing relevant information regarding its risk of bleeding. New endoscopic techniques, accessories and compounds make the minimally invasive treatment suitable for a vast array of lesion types. Our main goal in this chapter is to summarize the main presentation of lesions at risk of bleeding, briefly classify them according to the gastrointestinal segment and finally detail the endoscopic treatment options currently available.

Therapeutic endoscopy significantly reduced mortality from upper gastrointestinal bleeding. Most common causes of lower gastrointestinal bleeding are: colon cancer, diverticulosis, colon polyps, inflammatory bowel disease, hemorrhoids, anal fissures and angiodysplasia. Digestive bleeding diagnosis strategy requires rapid clarification of the following elements: recognition of gastrointestinal bleeding, specifying the location of bleeding, assessment of its severity, specification of the etiology of bleeding and patient's risk factors. Early diagnosis of the cause of bleeding and endoscopic hemostasis reduced the need for hospitalization, blood transfusions and emergency surgery.

Keywords: endoscopic hemostasis, gastrointestinal, endoscopic treatment, colon cancer

1. Introduction

Digestive endoscopy represents an essential diagnostic and curative tool used when presented with a suspicion of gastrointestinal (GI) bleeding. Its role is not only confined to primary detection but also to establishing the severity of a lesion and providing relevant information regarding its risk of bleeding. New endoscopic techniques, accessories and compounds make the minimally invasive treatment suitable for a vast array of lesion types. Our main goal in this chapter is to summarize the main presentation of lesions at risk of bleeding, briefly classify them according to the gastrointestinal segment and finally detail the endoscopic treatment options currently available.

2. Endoscopic semiology

In general, we can describe four main types of gastrointestinal lesions that may present a risk of bleeding.

Hemorrhagic lesions are described as either *active injury bleedings* or the *stigmata of bleeding*. The first type is found mainly as point hemorrhagic lesions that bleed. They appear in uremic gastritis, some toxic or drug-induced gastritis. Bleeding stains are described as areas of 2-5 mm in diameter, highlighted in alcohol or NSAIDs-induced gastropathies. A hemorrhagic area of approximately 5-20 mm can present active bleeding, either diffuse, with areas of normal mucosa, caused by capillary bleeding, or bleeding from a vessel [1], either continuous (vein) or pulsating (arterial). *The stigmata of bleeding* persist after the bleeding has stopped, until full healing occurs. Re-bleeding can be predicted from injuries: ulcers, varices, hemorrhagic erosive gastritis [1-3].

They are described as petechial lesions (small hyperemic points that generally do not bleed), bruising (blue area of the mucosa caused by extravasated blood) and blood clots (blood vessel coated with a clot).

2.1. Flat lesions at risk of bleeding

The most commonly described is erythema, reddish appearance of the mucosa. Aftae are very superficial erosions covered by fibrin debris with peripheral leukocytes and surrounded by an intensely hyperemic halo. Deposits are usually purulent, a thin layer under which erosions are usually found. Angiodysplasia lesions are dilated vascular structures, usually pulsatile, and with multiple ramifications.

Vascular protrusions and protruding lesions at risk of bleeding are described as hemangiomas - clusters of capillaries and veins produced by anarchic proliferation; varices - dilated veins located in the submucosa, which protrude to the surface mucosa and have tortuous paths [4] and polyps (polypoid lesions - Figure 1) that may have an ulcerated surface, covered with detritus, or active bleeding.

http://dx.doi.org/10.5772/61192

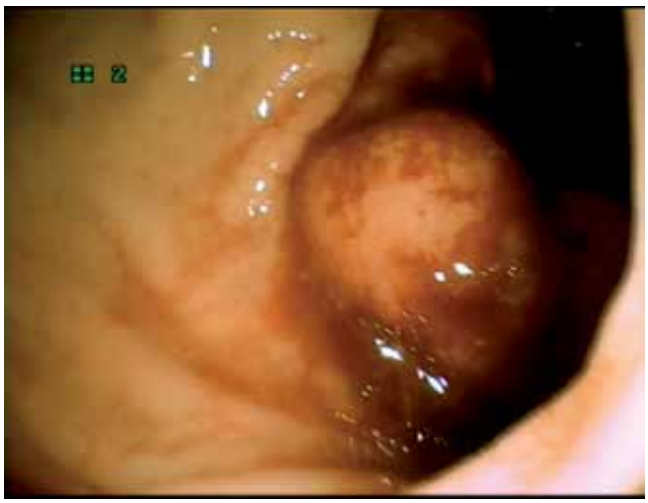

Figure 1. Bleeding polyp of the sigmoid

Excavated injury at risk of bleeding are either cracks, ulcerations or ulcers. Cracks are extremely narrow linear ulcerations that generally go deep and may be covered by necrotic or hemorrhagic debris. Ulcerations are superficial, up to 2 mm deep, with a more or less regular outline, having a diameter of 4-5 mm; they are generally acute. The ulcer (niche) represents a loss of substance above 2-3 mm, with generally well-cut edges. Their shape varies depending on the age of the lesion.

3. Lesions at risk of bleeding

3.1. Esophageal lesions

Esophageal varices are venous dilatations that continue gastric coronary veins, piercing the wall of the esophagus above the cardia or in the submucosa. They usually appear in portal hypertension of any etiology. Their color varies with depth: the deepest appear white, while superficial varicose veins display a more bluish hue.

The caliber of esophageal varices varies depending on peristalsis, being more turgid and more tortuous during movement. The classical classification of esophageal varices identifies 5 degrees, depending on size: Ist grade - protrude into the lumen, veins are tortuous, with sizes up to 1-1.5 mm; IInd grade have dimensions between 2 and 4 mm and 3-4 mm beyond the mucosa plan; IIIrd grade are more turgid, have more than 5 mm in diameter and may occupy half of the esophageal lumen; IVth grade varices are 6-7 mm in size, exceeding half of the esophageal lumen, without occluding it; Vth grade are larger than 6-7 mm (giant varices) and are extremely dilated, frequently occluding the lumen of the esophagus.

3.1.1. Early esophageal cancer

Malignant lesions limited to the mucosa and submucosa, with or without lymph node metastases. Upper endoscopy can highlight different aspects: background mucosa erosion, surface hyperemia and erythema, slightly elevated plates with grainy surfaces, or confluent plaques which give the appearance of "orange peel" edema and congestion as red spots that bleed easily. Cancer superficial erosion is friable, bleeding when touched by the endoscope, and represents the most common lesion. It can produce an enteric fistula with massive aortic bleeding which is often fatal.

3.1.2. Candidal esophagitis

Flat lesions with very thick fibrin and leukocyte deposits; underneath, we can find granulation tissue, hyperemia, spontaneous bleeding.

3.2. Pathology of the stomach

Congestive mucosa is characterized by hyperemia, edema and exudation; may be the result of irritation, functional disorders and gastritis. It can appear as red freckles distributed throughout the gastric mucosa; mosaic-like (multiple areas of erythema, bordered by a whitish reticular network); cherry-red spots, representing confluent areas of diffuse bleeding; black-brown spots representing hematin, indicating an old bleedings.

Hemorrhagic gastritis is defined by the presence of hemorrhagic spots, either as ecchymosis areas or diffuse gastric bleeding.

3.3. Vascular abnormalities of the colon

Angiodysplasia is diagnosed especially in the elderly, often in the cecum and ascending colon. **Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)** is characterized by small lesions that are found on the skin, lips and the entire gastrointestinal tract.

Hemangiomatosis cavernous is a rare condition characterized by cavernous hemangiomas of the skin and is bluish in color in the gastrointestinal tract, including the colon. Cavernous hemangiomas may be located remote from the rectum.

Varices can be located on any segment of the colon or rectum, more frequently in patients with portal hypertension. Varicose veins of the anorectal junction are considered hemorrhoids.

Ischemic colitis can sometimes be encountered during the diagnosis of acute rectal bleeding. Endoscopic changes are varied and depend on the severity and duration of ischemia. Endoscopy finds pale mucosa with multiple petechiae and hemorrhagic necrosis of superficial areas. Similar ulcers may occur in late Crohn's disease (Figure 2), only less deep. Usually, these cases do not reach endoscopy as they present as an acute surgical abdomen, soliciting emergency intervention.

http://dx.doi.org/10.5772/61192

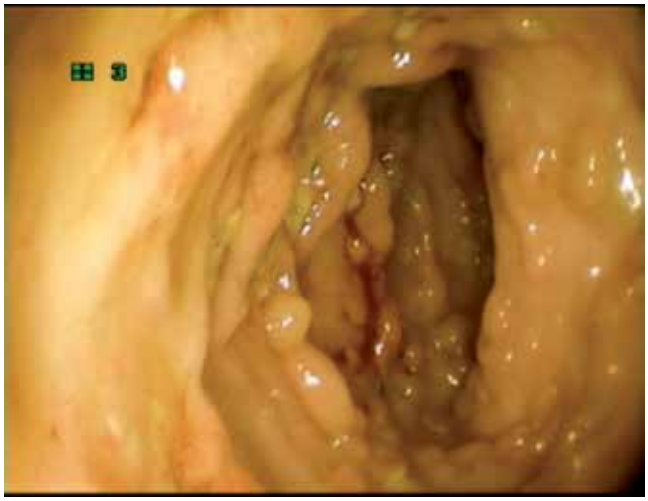

Figure 2. Crohn's disease

3.3.1. Bleeding after endoscopic procedures

Bleedings are rare and usually minor after gastrointestinal endoscopy diagnostic procedures, unless associated with anticoagulant therapy, thrombocytopenia and portal hypertension. Postbiopsy bleedings are minor and stop spontaneously. Upper endoscopy with biopsy diagnosis is generally a safe procedure, even at a platelet count of 20,000/mmc; currently available data suggest that anticoagulation therapeutic target in appropriate doses and treatment with standard doses of NSAIDs are not associated with increased risk of bleeding. However, both biopsy and therapeutic procedures should be avoided if the platelet count is below 20,000/mmc or if the anticoagulant treatment is overdosed.

4. Endoscopic therapeutical options

4.1. Endoscopic hemostasis

Endoscopic hemostasis is one of the most common applications of interventional endoscopy procedures [5], due to the bleeding frequency and vital digestive and immediate risk that these entail. Endoscopic hemostasis requires techniques used in combination to stop gastrointestinal bleeding. Correct identification of the source of bleeding is a very important step as approximately 2% of lesions are not identified at the first endoscopy. Once the source of bleeding is identified, the next step is the application technique and hemostasis and the initiation of the pharmacological treatment. "Second-look" endoscopy, defined as endoscopic revaluation 24-48 hours after successful hemostasis, is a controversial practice.

The main techniques used for endoscopic treatment of digestive bleeding are: **endoscopic ligation**, **injection techniques** (such as injection of adrenaline or of sclerosing substances);

laser therapy; **argon plasma**; **thermocoagulation**; **electrocoagulation**; **mechanical techniques** (metal clips, sewing equipment or equipment for mechanical suture).

Endoscopic ligation is indicated in digestive bleeding caused by rupture of esophageal varices, Dieulafoy's lesions rupture of varices stomach (lower but effective). It is based on fitting a Saeed ligator multiband type (4-6-8 ligatures) at the end of therapeutic endoscope before the examination. Consists of a plastic cylinder that is fitted with elastic bands that are issued by tractioning a wire (non-metal or metal) into the biopsy channel. Ligatures of the wire are at risk of trauma on channel biopsy, although this risk is reduced. Complications are possible: postligature ulcerations (higher risk for varicose gastric), bacteremia, postligature pain and strictures.

Endoscopic sclerotherapy uses a wide range of sclerosing agents [6, 7]: 70 degrees alcohol or absolute alcohol sodium morrhuate, ethanolamine oleate and polidocanol. The main indication is represented by gastric or esophageal varices. Alcohol is cheaper, but most endoscopy centers in developed countries are using polidocanol. To gastric varices, the preferred technique is injecting N-butyl-2 cyanoacrylate histoacryl (super glue) through a special catheter. The main risks are the pulmonary embolism, as well as sticking of the biopsy channel of the catheter, which resulted in serious damage in endoscope and even irreversible. Varicose esophageal varices may be associated with risk of stricture of bacteremia and chest pain.

Sclerosing technique is relatively as simple as endoscopic ligation. Varicose is done by entering the sheath sclerotherapy biopsy channel, with the needle inside (to avoid damage to the biopsy channel). At the end of the sheath when viewing off peak endoscope, remove the needle from the sheath and inject about 1-2 ml tangent in variceal path immediately below the bleeding, repeating the procedure in the four quadrants. The maneuver can be repeated if bleeding is not found to stop within 1-2 minutes. Higher doses may be associated with local necrosis.

After the endoscope advances to the identified place, the endoscopist can place the tip of the endoscope immediately in place, as close as possible to the variceal path of the ligation cylinder. Maintaining aspiration, one can apply a ligature by tractioning the ligation wire, continuing for 2-3 seconds after the aspiration application of the ligature. Then repeat the procedure in the four quadrants and the variceal tracts projecting from the lower to the portion on top of the esophagus.

Injection of hemostatic solutions is useful in gastric ulcers, duodenal or anastomotic, Mallory-Weiss syndrome even more effective in bleeding tumors or bleeding Dieulafoy's lesions postpolipectomy [7]. The 1/10000 adrenaline solution used is prepared by diluting 1 ml adrenaline in 1/1000 9 ml saline. The needle sheath channel biopsy is used as in sclerotherapy of esophageal varices. Injection of adrenaline around the lesion is bleeding in all four quadrants, starting with the most distal point. The favorable effect is visible through bleaching and raising the lining around the area where the injection is stopping bleeding. Electrocoagulation consists in the application of high-power frequency of the tissue directly, resulting in a local heat of 100°C. Thus, the bleeding vessel is closed by coagulation necrosis of the surrounding tissue and the vascular wall. Efficiency of the method is shown in 80-95% of patients. The multipolar electrocoagulation version is the most common today, consisting of applying three

http://dx.doi.org/10.5772/61192

equally spaced bipolar electrodes. Multipolar electrocoagulation eliminates some drawbacks of proof pole as unpredictable depth of tissue damage, adherence of tissue and mobilization of clots.

The effectiveness of coagulation is expressed by flattening or even depression visible vessel, which indicates the need for pressure, otherwise rebleeding might occur. Both coagulation and polypectomy require an endoscopy laboratory device electrosurgical cutting and coagulation current. Thermocoagulation is defined as a source of bleeding and coagulation by means of an aluminum spatula coated with Teflon. The tool can be irrigated with a jet of water to prevent the accumulation of debris and tissue clots on it. The method of coagulation is similar to electrocoagulation.

Mechanical techniques include applying metallic clips and use of sewing machines and equipment for mechanical suture. The available applicators clips are placed on the biopsy channel and are applied by pressing the clip, then applicator detachment clip applicator is withdrawn, with the clip remaining at the bleeding.

The primary indication is bleeding from larger vessels, but can be used for closure of holes or iatrogenic postpolipectomy perforation. Both for hemostasis as well as for the treatment of perforations recommend using multiple clips at the same lesion site.

Argon plasma coagulation (APC) requires argon plasma apparatus with argon cylinders. Application is made from a distance of a few millimeters, without the need for direct contact with the mucosa. Safe coagulation is possible because the effect is limited to 3 mm depth [8]. Introducing excess gas is one of the adverse effects. The major indication is represented by angiodysplasia or diffuse bleeding from the rectum, but can also be used for palliative purposes such as radical digestive tumors. Adenomatous tissue remnants can be destroyed, postpolipectomy being useful in supplementing it. The laser can stop the bleeding by vaso-constrictive properties associated with protein wall degradation and dehydration, but its use in endoscopic hemostasis is reduced.

5. Endoscopic treatment of some of the most prominent gastrointestinal bleedings

5.1. Endoscopic treatment of variceal bleeding

Endoscopic sclerotherapy involves injecting sclerosing substances that cause coagulation necrosis and induces instantaneous and local thrombosis. Endoscopic sclerotherapy is superior to conservative measures, with a success rate of about 90% for the control of variceal bleeding; early rebleeding frequency decreases and increases survival [9].

Thrombosis of esophageal varices is achieved by endoscopic injection of sclerotic agents (absolute alcohol, sodium morrhuate 5%, ethanolamine oleate 5-10%, 1-2% sodium tetradecyl sulfate) just above the esogastric junction. Paravariceal injections are performed, both intra-

variceal or combinations. Comparative studies of the effectiveness of different substances are numerous, but the relative effectiveness of different substances is not clear.

The risk of rebleeding and complications is high. The most common cause of esophageal ulcers appears to be massive rebleeding and mortality of 2-3%. Almost all patients have fever, transient dysphagia and chest pain. Other possible complications are chest pain, aspiration pneumonia, pleural effusions and mediastinitis [10, 11]. Frequency of complications depends on the experience of the operator and is proportional to the amount of sclerosant injected; and mortality induced complications are between 2-5%.

Endoscopic variceal ligation uses small rubber rings or strips of nylon for varicose veins occlusion, promoting hemostasis by physical contraction, followed by local thrombosis. Ligation with multiple lanes is used which allows strangulation of esophageal tract, followed by local necrosis. Variceal path is drawn in clear plastic a cylinder loaded with elastic bands, followed by the release of the first bands. The effectiveness of elastic ligatures is similar to sclerotherapy to control acute bleeding esophageal varices rupture, the success rate of approximately 90%. The number of sessions required for eradication is significantly lower compared with sclerotherapy.

Complications are significantly reduced and mainly consist of dysphagia or esophageal ulcers. However, esophageal ulcers laid after ligation tend to be small, with low risk of perforation and strictures. Aspiration pneumonia is a complication of endoscopic examination in the context of upper gastrointestinal bleeding [12]. A recently described complication consisted of ligation circumference esophageal strictures after pushing to form a band with the endoscope into the stomach [13].

Compared with sclerotherapy, endoscopic ligation gives better results in terms of frequency of complications, prolonged survival but also a better control of active bleeding [14-16]. Meta-analysis of published studies demonstrated that esophageal varices ligatures are significantly more effective than sclerotherapy variceal rebleeding prevention, with fewer sessions needed on average for eradication and fewer major complications [17]. Endoscopic ligation efficiency of endoscopic sclerotherapyis superior to the use of somatostatin or octreotide drug therapy [16, 17]. Usually, six elastic bands are used in the ligation sessions. Using a higher number of bands is not associated with a higher efficiency and is accompanied by an increased time of the procedure [18].

Endoscopic treatment by ligation of esophageal varices is more effective than medical therapy in active variceal bleeding and to prevent early rebleeding [19]. Other options included the use of cutouts (Endoloop) compared with elastic ligatures that appeared to have a similar efficiency [20]. Plastic mini-loops (nylon) are passed through the biopsy channel and placed on the inside of the cylinder. Similar elastic bands in variceal path are drawn into the transparent cylinder, and then loop is detached and tightened. Similar elastic bands and sclerotherapy detachable loops are associated with these possible complications: esophageal ulcers laid, laid pierce, strictures and infections. Although the authors consider cutouts as an option compared to treatment with elastic ligatures, this method has not gained popularity due to technical difficulties using cutouts in acute hemorrhage.

http://dx.doi.org/10.5772/61192

5.2. Gastric varices

In esogastric varices Type I (continuation of esophageal along the lesser curve gastric), treatment should be similar to HDS treatment of esophageal varices rupture. If gastric varices are isolated using adhesive agents (N-butylcyanoacrylate, isobutyl-2-cyanoacrylate and thrombin), endoscopic ligation compared with sclerotherapy and alcohol is superior to a better initial control of bleeding and rebleeding rate of less [21, 22]. In a recent pilot study of a new adhesive agent, 2-octyl cyanoacrylate appears to be as effective in obtaining hemostasis and prevents rebleeding from initial background varices [23].

Other invasive treatments (TIPS, surgical shunts, splenectomy, retrograde transvenous obliteration balloon occlusion) are still used. An attractive option was to use elastic ligatures or cutouts, which are being evaluated, taking into account the low efficiency of sclerotherapy.

Endoscopic obstruction by 2-cyanoacrylate isobutyl (bucrylate) or 2-cyanoacrylate N-butyl-(histoacryl) is used for large esophageal or gastric varices. The mechanism of action consists in polymerization and rapid solidification after intravariceal injection. Complications include emboli (lung, kidney, brain, etc.) in up to 5% of the patients, the passage of the adhesive through the inferior vena cava or gastrorenal or damage to the endoscope (channel occlusion) or needle impaction varices. Dilution with lipiodol is preferred since the polymerization process delays by 20 sec [24].

In the absence of tissue adhesives, conventional endoscopic techniques involve the use of elastic ligatures with or without combinations with sclerotherapy. Sclerotherapy classic sclerosing substance is not currently listed, complications are due to large and high frequency of severe and fatal rebleeding [24]. Elastic ligatures combined use of sclerotherapy with cyanoacrylate seems to be superior to simple methods [25, 26].

Combined treatment (ligatures + sclerotherapy) in patients with gastric variceal bleeding assets seems very promising, 100% taking into account initial hemostasis (after ligation and injection of 1% polidocanolinto the neighboring submucosa) [27]. These promising results will be confirmed in prospective studies with large numbers of patients. Retrograde transvenous obliteration occlusion balloon is a method recently used with good results in patients with gastric and gastrorenalvarices [28, 29]. Left adrenal vein is cannulated through a retrograde path from the right femoral vein or right internal jugular vein. After vein occlusion, left renal venography is performed and sclerosating agents are injected (ethanolamine oleate) mixed with iopamidol, with radiological control up to complete filling of gastric varices. Compared to treatment with TIPS, transvenous obliteration has the same proportion of hemostasis, rebleeding and encephalopathy, the major drawback being that it cannot be performed in patients with gastrorenalvarices [18].

5.3. Non-variceal upper gastrointestinal bleedings

Endoscopic treatment allows definitive stop of active bleeding in over 90% of the cases [30-32]. Meta-analysis of published studies have clearly indicated that active bleeding stops endoscopic treatment in most cases and significantly reduces the frequency of rebleeding, transfusion requirements, emergency surgical interventions and mortality [33-35]. Mortality is

directly correlated with rebleeding, both dependent on different variables and clinical stigmata of bleeding as defined by Forrest classification. A consensus was reached that endoscopic treatment must be performed only in patients with increased risk of bleeding or rebleeding and thus increased mortality [36].

Patients with active bleeding (Forrest Ia and b) and visible vessel (Forrest IIa) are treated by endoscopy. Although initial studies recommended treatment of ulcers with adherent clot (Forrest IIb), several recent studies have demonstrated these patients require treatment by endoscopic removal of the adherent clot [37, 38]. Patients with pigment spots in the ulcer crater (Forrest IIc) or clean base (Forrest III) did not receive endoscopic treatment; with a low frequency of rebleeding, a proton pump inhibitor treatment is sufficient. Different endoscopic hemostasis treatments are currently available for endoscopic hemostasis: injection (adrenaline or sclerosing agents), thermal methods (argon plasma coagulation or multipolar) or mechanical methods (clips, ligatures elastic). The primary hemostasis is achieved in over 95% of cases, rebleeding seen in 5-10% of patients, respectively mortality of approximately 5% [39]. However, there is an extremely high variability of methods used and results obtained from different centers, probably due to experienced endoscopists and risk category included for patients (age, associated diseases, etc.) [40].

5.4. Hemostasis injection

Endoscopic hemostatic treatment by injection is applied using a metal retractable catheter needle, which is inserted through the biopsy channel of the endoscope. Live view of the needle tip allows precise positioning of endoscopic control. If the lesions are located at tangential face of needle, the needle can be removed to cling to the lining and to facilitate positioning catheter. Injection of epinephrine 1:10,000 is used frequently in ulcer bleeding but can be used on other types of non-variceal lesions). Injection of epinephrine 1:10,000 has very few risks and complications. The risk of perforation is also negligible. According to a recent study, it was shown that injection of submucosa adrenaline can cause significant hemodynamic changes that can lead to severe cardiac adverse effects [41]. In this regard, monitoring heart after administration of epinephrine is the recommended cautious attitude more especially when used in large doses. In the treatment of bleeding lesions, esophagus total dose of adrenaline should be carefully titrated and should be used with a minimum dose that can achieve hemostasis. Sclerosing substances are generally reserved for hemostasis in patients with variceal bleeding, especially for esophageal varices. Histoacryl (N-butyl-2-cyanoacrylate) is a tissue adhesive which instantly coagulates in contact with blood. Injection of the varices histoacryl determines the solidification path of the variceal occlusion by inducing thrombosis vein, being used mainly for gastric varices. Rubber band ligation is not effective in mucous coating and is gradually affected by exulceration favoring the use of extrusion solidified adhesive, with the emergence of a profound ulcer. The main complication consists of glue embolization at brain and lung.

Thermal hemostasis methods can be divided into direct contact and non-contact thermal coagulation. Non-contact coagulation refers to the use of laser treatment or argon plasma coagulation jet. Coagulation is used in baked, i.e. non-variceal, hemorrhage when a vessel is visible. There are significant differences between monopolar coagulation probes, bipolar and

http://dx.doi.org/10.5772/61192

multipolar heater samples and the mechanism of action is similar [42]. Area bleeding or visible vessel is compressed while applying electrical or thermal energy in pulses that lasts up to 8 consecutive seconds. The preferable accessories are large (3.2 mm) and a current of 15-25 W. The application of thermal energy in the absence of compression of the vessel wall may worsen breakthrough of bleeding vessel wall. The risk of perforation is substantially increased in acute ulcers approached by thermal coagulation.

Argon plasma coagulation (APC) transmits heat to tissues through ionized gas and does not require direct contact probe to target lesion. APC cannula is placed 1-2 mm distance from target lesion and activated to induce coagulation of tissue surrounding surface. The risk of perforation is lower, excluding attachment of the cannula tube to the wall tract. Argon plasma coagulation is used for the treatment of superficial injury of vascular malformation type. In addition, APC was elastic ligatures used in combination with secondary prophylaxis variceal bleeding due to reduction of variceal recurrence. Although they are highly effective achieving hemostasis, mechanical devices are extremely difficult to place in lesions that are difficult to reach (small gastric curvature and posterior wall of the duodenum).

Metal clips are similar to surgical sutures and can be placed endoscopically under direct vision. Two to five clips are generally placed for achieving hemostasis in the area of bleeding or visible vessel. The main advantage lies in the absence of tissue damage and the possibility of using in deep ulcers or large blood vessels. Videos can also be used to close small punctures on them, although difficult to locate, especially when using tangential or ulcers central fibrosis.

Elastic ligatures are currently considered the treatment of choice for the rupture of esophageal varices. Elastic ligatures are particularly effective for stopping jet bleeding (spurting), although equally difficult to place in conditions like fibrosis of ulcers [43-45]. Placement is facilitated by the injection of mucosa adrenaline 1:10,000. Both clips as well as elastic ligatures are relatively easy to place and have good efficiency in cases of non-variceal HDS of due to non-ulcer: Mallory-Weiss syndrome, arteriovenous malformations, Dieulafoy's lesion, or bleeding postpolipectomy, such as endoscopic mucosa resection [46-48]. Rebleeding seems to be greatly reduced by using mechanical hemostasis (clips or ligatures) versus adrenaline injection in patients with Dieulafoy's lesions [49]. Removable clips were initially used to reduce bleeding occurring after the resection of formations protruding the mucosa, tailored with a plastic cylinder used for variceal bleeding. In patients with chronic colitis with HDS, non-variceal hemostasis is more effective in combination by applying heat treatment and injection.

Hemostasis techniques may be ineffective in a variable number of cases. In these situations, alternative techniques are used which include coagulation jet argon plasma (APC) or mechanical devices (metal clips, ligatures removable nylon elastic loops) [50-52]. Good results occur after placement of the ligatures, elastic, in particular small lesions (Dieulafoy's lesions, hemangiomas, small ulcers <1 cm, etc.).

5.5. Rebleeding and "second-look" endoscopy

Active bleeding cannot be controlled by endoscopic and it requires emergency surgical intervention [53]. Patients who rebleed after endoscopic treatment must repeat endoscopy to confirm the source of bleeding and bleeding stigmata. After rebleeding, endoscopic retreat-

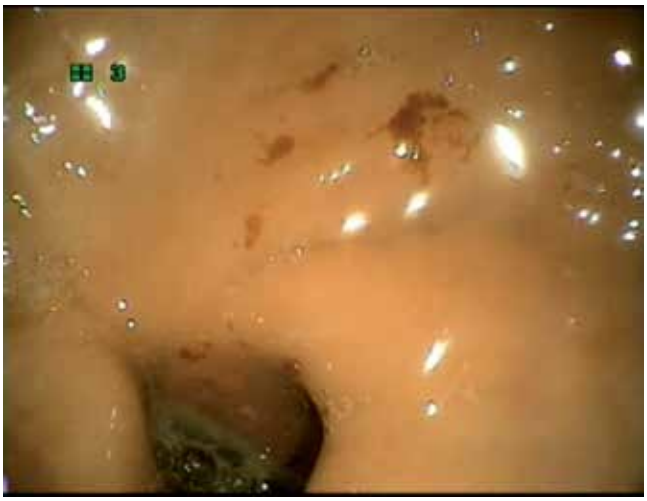

Figure 3. Gastric angiodysplasia and duodenal ulcer

ment intervention is comparable to surgical prognosis [54]. The management of rebleeding after endoscopic treatment and correct medical treatment depend largely on local expertise and clinical judgment [53]. Endoscopic or surgical treatment decision after rebleeding obviously depends on the age, associated diseases and bleeding stigmata. Thus, a patient duodenal ulcer with a giant rear face with stigmata of recent hemorrhage requires surgical intervention, while a young patient without leather rot associated with a small curvature gastric ulcer on endoscopy can be restated. "Second-look" endoscopy is controversial, published studies have demonstrated only a smaller proportion of rebleeding, but the same survival and required surgical intervention [55]. Repeat endoscopy is indicated in patients with clinical suspicion of rebleeding (hematemesis, melena, tachycardia, decreased pressure). Although some patients require direct surgical intervention, the majority of repeat endoscopy are indicated to confirm rebleeding [53].

5.6. Vascular malformations

Vascular malformations laid comprise several entities: angiodysplasia (Figure 3), telangiectasia (Osler-Weber disease, Rendu syndrome or Turner CREST) phlebectasia (varicosities and well-defined circular) and hemangiomas. Moreover, although endoscopically identified as a possible cause of bleeding, they cannot be differentiated based on endoscopic appearance. The diagnosis of leather rot are used and other imaging techniques such as angiography or, more recently, positron endoscopic optical coherence Doppler (Doppler optical coherence tomography) is a method that detects different vascular patterns [56].

Angiodysplasia (Figure 3) are found within 5% of gastrointestinal bleeding higher, being more common in the stomach, duodenum and proximal portion small intestine. Prevalence of angiodysplasia appears to be greater in patients with chronic renal insufficiency. Endoscopic treatment was performed along time with different methods (injection, multipolar electrocoa-

http://dx.doi.org/10.5772/61192

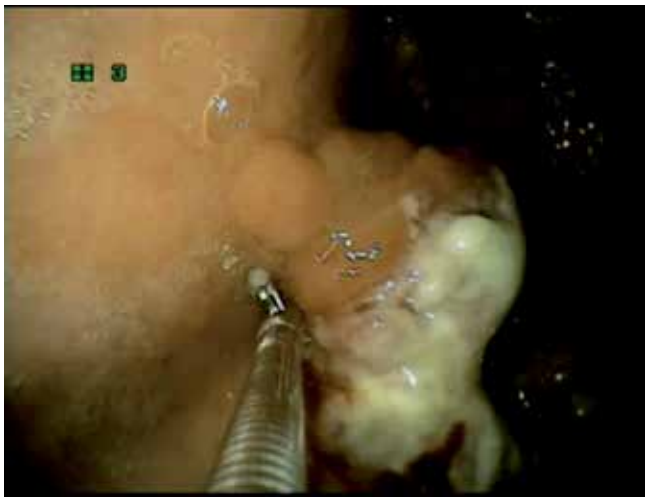

Figure 4. Gastric adenocarcinoma

gulation and bimechanical methods), but the degree of success is variable. Rebleeding is frequently encountered by all forms of treatment, due to the presence of lesions that are multifocal, inaccessible and the potential for the formation of new lesions [57]. The most common method remains bipolar coagulation and laser treatment Nd: YAG [58]. Recent studies have indicated the usefulness of eradication lesions using argon plasma coagulation (APC) [59]. Isolated gastric angiodysplasia can be treated with elastic ligatures [60]. Multiple other non-endoscopic treatments of angiodysplasia were tested with variable results: hormonal medication, administration of octreotide, antiangiogenic agents used in oncology and (thalidomide, lenalidomide bevacizumab, etc.), the management of acid aminocaproic [61-63]. Endoscopic treatment reduces the rebleeding and transfusion needs. Surgery is an indication only in cases with severe or acute hemorrhage in patients with severe anemia; persistent bleeding in the intestinal segment is usually well defined.

5.7. Gastrointestinal tumors

Gastrointestinal tumors are a common cause of non-variceal bleeding, most cases the gastric adenocarcinomas (Figure 4). Other tumors encountered are ampullary or duodenal tumor invasion of pancreatic head cancers, submucosal or metastatic tumors. Immediate survival of these patients is similar to other patients with non-variceal HDS, but prognosis term is reserved. Endoscopic treatment has limited benefits; endoscopic hemostasis has a role to delay until the intervention is definitive or palliative surgery. Inoperable patients may benefit from palliative treatment with laser or argon plasma.

5.8. Esophagitis and esophageal ulcers or contravention of junction esogastric

Reflux esophagitis occurs due to prolonged contact of contents of peptic esophageal mucosa and being characterized pathologically by esophageal mucosal inflammatory lesions that are

potential sources of bleeding [64]. 5% of reflux esophagitis and be complicated by gastrointestinal bleeding. It can be located at esogastric junction or mucosal metaplasia of Barrett's esophagus, requiring repeat biopsies to exclude esophageal cancer that can develop within the lesion. Reflux esophagitis occurs frequently in the presence of hiatal hernia. In the context of the presence of hiatal hernias, large Cameron ulcers can occur, which are longitudinal ulcers identified in approximately 1/3 of patients [65].

Esophagitis can occur during or after radiation treatment for lymphoma, lung cancer, breast cancer or other mediastinal malignancies. These patients have increased risk of developing esophageal cancer in a few years. Acute necrotizing esophagitis (black esophagus) is a particular form of severe damage to the esophagus, rarely met, but frequently associated with upper gastrointestinal bleeding. It generally appears in patients with severe general condition, with cancer or after severe infections.

5.9. Erosive gastritis and hemorrhagic gastropathy

Erosive gastritis stress and hemorrhagic gastropathy accounts for 25% of cases of non-variceal bleedings [64]. Stress gastritis generally occurs in patients with shock, burns, sepsis, severe trauma, multiple organ insufficiency after complicated surgical interventions and so on. In general, stress gastritis is characterized by the occurrence of multiple superficial gastric ulcers, with diffuse bleeding. These lesions are located initially at the back of the gastric body then extend throughout the gastric surface. In most patients the bleeding stops spontaneously, but medical treatment and angiographic or surgical excision may be necessary to a small fraction of patients [64]. Prophylaxis of stress gastritis is much more important, being necessary to prevent bleeding by increasing digestive intragastric pH above 4. Hemorrhagic erosive gastropathy consists of multiple erosive and subepithelial bleeding, endoscopic views, which may cause digestive bleeding. These injuries occur in different clinical circumstances, the most common being the intake of NSAIDs, aspirin and alcohol. Bleeding from gastric and gastropathy have low severity, stop spontaneously, and mortality is relatively low. Stop the NSAID or aspirin and patients are treated with standard PPI doses. Endoscopic treatment is not necessary.

Author details

Paul Mitrut, Liliana Streba*, Anca Oana Docea, Adina Kamal, Sorin Ioan Zaharie , Nicolae-Dragoș Mărgăritescu and Costin Teodor Streba

*Address all correspondence to: lilianastreba@gmail.com

University of Medicine and Pharmacy of Craiova, Romania

http://dx.doi.org/10.5772/61192

References

[1] Dennis MJ. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002;122(6):1620-30.

[2] Laine L, Cohen H, Sloane R, Marin MS, Weinstein WM. Interobserver agreement and predictive value of endoscopic findings H. pylori and gastritis in for normal volunteers. Gastrointest Endosc 1995;42:420-3.

[3] De Lange T, Larsen SL. Image Aabakken documentation of endoscopic findings in ulcerative colitis: photographs or video clips? Gastrointest Endosc 2005;61(6):715-20.

[4] Cotton PB, Williams CB. Recognition of lesions. In: Cotton PB, Wiliams CB. (eds.) Practical Gastrointestinal Endoscopy. The Fundamentals, fifth edition, Blackwell Publishing, 2003; pp. 49-53.

[5] Henrion J, Schapira M, Ghilain JM, et al. Upper gastrointestinal bleeding: what has changed during the last 20 years? Gastroentérol Cliniq Biologiq 2008;32:839-47.

[6] Celinski K, Cicho-Lach H, Mydro A, et al. Non-variceal upper gastrointestinal bleeding guidelines on management. J Physiol Pharmacol 2008;59(2):215-29.

[7] Aabakken L. Nonvariceal upper gastrointestinal bleeding. Endoscopy 2005;37:195-200.

[8] Celinski K, Cicho-Lach H. Therapeutic endoscopy in gastroenterology. J Physiol Pharmacol 2007;58(3):33-41.

[9] Sampliner RE. Barrett's esophagus: electrocoagulation. Gastrointest Endosc 1999;49:S17-9.

[10] Hayes PC, Ferenci P. Portal hypertension. Eur J Gastroenterol Hepatol 2001;13:307-8.

[11] Bhasin DK, Siyad I. Variceal bleeding and portal hypertension: new lights on old horizon. Endoscopy 2004;36:120-9.

[12] Bhasin DK, Malhi NJS. Variceal bleeding and portal hypertension: much to learn, much to explore. Endoscopy 2002;34:119-28.

[13] Saftoiu A, Ciurea T. Aphagia caused by accidental banding of the esophageal circumference: how much can we ligate? Endoscopy 2002;34:1030-1.

[14] Stiegmann GV, GoV JS, MichaletzOnody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992;326:1527-32.

[15] Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. Hepatology 1995;22:466-71.

[16] Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 1995;123:280-7.

[17] Gross M, Schiemann U, Muhlhofer A, Zoller WG. Meta-analysis: efficacy of therapeutic regimens in ongoing variceal bleeding. Endoscopy 2001;33:737-46.

[18] Ramirez FC, Colon VJ, Landan D, Grade AJ, Evanich E. The effects of the number of rubber bands placed at each endoscopic session upon variceal outcomes: a prospective, randomized study. Am J Gastroenterol 2007;102:1372-6.

[19] Vlavianos P, Westaby D. Management of acute variceal haemorrhage. Eur J Gastroenterol Hepatol 2001;13:335-42.

[20] Naga MI, Okasha HH, Foda AR, et al. Detachable endoloop vs. elastic band ligation for bleeding esophageal varices. Gastrointest Endosc 2004;59:804-9.

[21] Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. Am J Gastroenterol 2002;97:1010-5.

[22] Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology 2001;33:1060-4.

[23] Rengstorff DS, Binmoeller KF. A pilot study of 2-octyl cyanoacrylate injection for treatment of gastric fundal varices in humans. Gastrointest Endosc 2004;59:553-8.

[24] Mumtaz K, Majid S, Shah H, et al. Prevalence of gastric varices and results of sclerotherapy with N-butyl 2 cyanoacrylate for controlling acute gastric variceal bleeding. World J Gastroenterol 2007;13:1247-51.

[25] Joo HS, Jang JY, Eun SH, et al. Long-term results of endoscopic histoacryl (N-butyl-2-cyanoacrylate) injection for treatment of gastric varices—a 10-year experience. Korean J Gastroenterol 2007;49:320-6.

[26] Sugimoto N, Watanabe K, Watanabe K, et al. Endoscopic hemostasis for bleeding gastric varices treated by combination of variceal ligation and sclerotherapy with N-butyl-2-cyanoacrylate. J Gastroenterol 2007;42:528-32.

[27] Arakaki Y, Murakami K, Takahashi K, et al. Clinical evaluation of combined endoscopic variceal ligation and sclerotherapy of gastric varices in liver cirrhosis. Endoscopy 2003;35:940-5.

[28] Imazu H, Seewald S, Omar S, Zhong Y, Soehendra N. Endoscopic treatment for portal hypertension: what's new in the last 12 months? Endoscopy 2005;37:116-21.

[29] Choi YH, Yoon CJ, Park JH, et al. Balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding: its feasability compared with transjugular intrahepatic portosystemic shunt. Korean J Radiol 2003;4:109-16.

[30] Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27.

[31] Lichtenstein DR. Nonvariceal upper gastrointestinal hemorrhage. In: Wolfe MM. (ed.) Therapy of Digestive Diseases, W.B. Saunders, 2000; 10: pp. 127-152.

[32] Stollman NH, Putcha RV, Neustater BR, et al. The uncleared fundal pool in acute upper gastrointestinal bleeding: Implications and outcomes. Gastrointest Endosc 1997;46:324-7.

[33] Sacks HS, Chalmers TC, Blum AL et al. Endoscopic therapy: an effective therapy for bleeding peptic ulcers. JAMA 1990;264:494-9.

[34] Cook DJ, Guyatt GH, Salena BJ, Laine L. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Gastroenterology 1992;102:139-48.

[35] Chung SC. Peptic ulcer bleeding. Am J Gastroenterol 2001;96:1-3.

[36] Bini EJ, Cohen J. Endoscopic treatment compared with medical therapy for the prevention of recurrent ulcer hemorrhage in patients with adherent clots. Gastrointest Endosc 2003;58:707-14.

[37] Jensen DM, Kovacs TO, Jutabja R, et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. Gastroenterology 2002;123:407-13.

[38] Laine L, Stein C, Sharma V. A prospective outcome study of patients with clot in an ulcer and the effect of irrigation. Gastrointest Endosc 1996;43:470-3.

[39] Church NI, Palmer KR. Ulcers and nonvariceal bleeding. Endoscopy 2003;35:22-6.

[40] Mahadeva S, Linch M, Hull M. Variable use of endoscopic hemostasis in the management of bleeding peptic ulcers. Postgrad Med J 2002;78:347-51.

[41] Von Delius S, Thies P, Umgelter A, et al. Hemodynamics after endoscopic submucosal injection of epinephrine in patients with nonvariceal upper gastrointestinal bleeding: a matter of concern. Endoscopy 2006;38:1284-8.

[42] Stiegmann GV, GoV GS. Endoscopic esophageal varix ligation: preliminary clinical experience. Gastrointest Endosc 1988;34:113-7.

[43] Koutsomanis D. Endoscopic ligation in ulcer bleeding: a controlled trial. Endoscopy 1995;27:S18.

[44] Tseng C, Burke S, Connors P, et al. Endoscopic band ligation for treatment of nonvariceal upper gastrointestinal bleeding. Endoscopy 1991;23:297-8.

[45] Matsui S, Inou I, Takahei K, et al. Endoscopic band ligation for hemostasis of nonvariceal upper gastrointestinal bleeding. Endoscopy 1996;28:S67.

[46] Soehendra N, Sriram PVJ, Ponchon T, Chung SCS. Hemostatic clip in gastrointestinal bleeding. Endoscopy 2001;33:172-80.

[47] Abi-Hanna D, Williams SJ, Gillespie PE, et al. Endoscopic band ligation for non-variceal upper gastrointestinal hemorrhage. Gastrointest Endosc 1998;48:510-4.

[48] Wong RM, Ota S, Katoh A, et al. Endoscopic ligation for non-esophageal variceal upper gastrointestinal hemorrhage. Endoscopy 1998;30:774-7.

[49] Chung IK, Kim EJ, Lee MS, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc 2000;52:721-4.

[50] Chau CH, Siu WT, Law BKB, et al. Randomized controlled trial comparing epinephrine injection plus heat probe coagulation versus epinephrine injection plus argon plasma coagulation for bleeding peptic ulcers. Gastrointest Endosc 2003;57:455-61.

[51] Chou Y-C, Hsu P-I, Lai K-H, et al. A prospective, randomized trial of endoscopic hemoclip placement and distilled water injection for treatment of high-risk bleeding ulcers. Gastrointest Endosc 2003;57:324-8.

[52] Matsui S, Kamisako T, Kudo M, et al. Endoscopic band ligation for control of nonvariceal upper GI hemorrhage: comparison with bipolar electrocoagulation. Gastrointest Endosc 2002;55:214-8.

[53] Targownik LE, Murthy S, Keyvani L, Leeson S. The role of rapid endoscopy for high-risk patients with acute nonvariceal upper gastrointestinal bleeding. Can J Gastroenterol 2007;21:425-9.

[54] Lau JY, Sung JJY, Lam T, et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999;340(10):751-6.

[55] Rollhauser C, Fleischer DE. Nonvariceal upper gastrointestinal bleeding: an update. Endoscopy 1997;29:91-105.

[56] Yang VX, Tang SJ, Gordon ML, et al. Endoscopic Doppler optical coherence tomography in the human GI tract: initial experience. Gastrointest Endosc 2005;61:879-90.

[57] Lichtenstein DR. Nonvariceal upper gastrointestinal hemorrhage. In: Wolfe MM. (ed.) Therapy of Digestive Diseases, W.B. Saunders, 2000; 10: pp. 127-152.

[58] Rollhauser C, Fleischer DE. Upper gastrointestinal nonvariceal bleeding: a review covering the years 1996-1997. Endoscopy 1998;30:114-25.

[59] Delis V, Balatsos V, Vamvakousis V, et al. Elastic band ligation for gastric angiodysplasias. Endoscopy 1996;28:S65.

[60] Mulder CJJ, den Hartog G, Thies JE. Pilot experience with argon plasma coagulation in gastrointestinal endoscopy. Gastrointest Endosc 1996;43:54-6.

http://dx.doi.org/10.5772/61192

[61] Lewis B, Salomon P, Rivera-MacMurray S, et al. Does hormonal therapy have any benefit for bleeding angiodysplasia? J Clin Gastroenterol 1992;15:99-103.

[62] Aabakken L. Nonvariceal upper gastrointestinal bleeding. Endoscopy 2001;33:16-23.

[63] Saba HI, Morelli GA, Logrono LA. Treatment of bleeding in hereditary hemorrhagic telangiectasia with aminocaproic acid. N Engl J Med 1994;330:1789-90.

[64] ASGE Standards of Practice Committee. ASGE guideline: the role of endoscopy in acute non-variceal upper GI hemorrhage. Gastrointest Endosc 2004;60:497-503.

[65] Lin CC, Chen TH, Ho WC, Chen TY. Endoscopic treatment of a Cameron lesion presenting as life-threatening gastrointestinal hemorrhage. J Clin Gastroenetrol 2001;33:423-4.

Chapter 5

Natural Orifice Translumenal Endoscopic Surgery of the GastroIntestinal Tract

Abdulzahra Hussain

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60552

Abstract

Research Focus - NOTES is a new technique that faces numerous challenges. Current technology, training and research activities are conducted to make it a safe and effective minimal access technique.

Research Methods Used - This chapter is based on the current evidence of published NOTES studies. Medline search is conducted through November to December 2014, including English literatures only. The search words are NOTES, natural orifice translumenal endoscopic surgery, hybrid NOTES and hybrid natural orifice translumenal endoscopic surgery; additional search words are specific for the titles like NOTES gastric, NOTES oesophageal, NOTES biliary, NOTES cholecystectomy, NOTES pancreatic, NOTES small bowel, NOTES colorectal and NOTES appendicectomy. Animal and human studies are selected after 2008. Small studies are excluded unless they report a novel approach or a new procedure.

Results/Findings of the Research - There is development in the technology by installing new platforms, instruments and closure devices to add more safety and security. There is also development in training and research activities across the continents; a number of NOTES procedures are performed safely on human beings including cholecystectomy, appendicectomy, peritoneoscopy, POEM and other procedures. Feasibility studies are conducted on animal and human cadaver models including numbers of complex procedures.

Main Conclusions and Recommendations - NOTES is evolving and gaining popularity. The growth rate however is slowed by challenges of the need for an ideal working platform and closure devices that are easy to use, cheap and time effective, in addition to the dedicated effective training.

Keywords: Upper GI NOTES, Lower GI NOTES, Oesophageal NOTES, Gastric NOTES, Duodenal NOTES, Liver NOTES, Pancreatic NOTES, Splenic NOTES

1. Introduction

Modern endoscopy began in 1805, when Phillip Bozzini first used a system to visualise the inside of the rectum and bladder through a mirror, a candle and a double-lumen ureteral catheter. The first source of inner light was invented by Bruck [1]. In 1878, Maximilian Carl-Friedrich Nitze introduced the first working cystoscope that contained a prismatic lens system and a channel through which you could insert a ureteral catheter, conducted in collaboration with Joseph Leiter [2]. Diagnostic methods of gastrointestinal tract have been evolving using flexible endoscopy. Dimitrij Oscarovic Ott (1855–1929) can undoubtedly be called the true pioneer of laparoscopy, especially of natural orifice translumenal endoscopic surgery (NOTES). In 1901 already he performed abdominal examinations via a transvaginal (Tv) access calling this procedure 'ventroscopy' [3]. In 1954 Hopkins made a crucial development by the idea of incorporating the light into scopes using the concept of multiple lenses separated by a room of air. Hopkins could never make the fibrescope, and it was a South African, Basil Hirschowitz, who made the first flexible fibreoptic gastroscope using Hopkins's idea [4]. Endoscopic retrograde cholangiopancreatography (ERCP) which was developed in 1968 and endoscopic ultrasound (EUS) in the 1980s are important milestones. With the development of sophisticated flexible scopes, it became feasible to conduct certain diagnostic and therapeutic GI procedures. Anthony Kalloo in 2000 reported the first peritoneoscopy on pigs [5]. Gastrointestinal (GI) NOTES is a further development in the minimal access surgery (MAS). It has been received by surgical community with scepticism similar to what happened with the first laparoscopic cholecystectomy (LC) when Muhe introduced it for the first time to the German Surgical Society in 1985. In 2004 Rao and Reddy performed the first transgastric (Tg) appendicectomy [6]. In 2012, authors considered that rigid standard laparoscopy provided better organ visualisation, better lesion detection and better biopsy capability than the transgastric (Tg) and transrectal (Tr) NOTES approaches [7], and that is expected as NOTES still undergo refining and development which should push for more efforts to overcome these challenges. In spite of uncertainty, GI NOTES proved itself for a number of procedures that are applied in elective and emergency settings with significant contribution to improve the care and attained a high level of patient satisfaction and most importantly a great scale of safety and efficacy. The GI NOTES is gaining popularity but at slower rate compared to LC. It has been limited to the university institutions and big teaching tertiary centres across Europe, America and Asia. Nevertheless, large series are reported on human beings. Many centres are conducting feasibility studies on animals as well as cadavers and patients. Several obstacles are preventing the wide applications of NOTES. Of these is the need for advanced endoscopic and laparoscopic skills, infrastructure setting, funding and local health authority approval and health systems bureaucracy. Germany reports the highest number of human NOTES procedures in the Europe, while the USA is the leading state in the American continent.

http://dx.doi.org/10.5772/60552

1.1. Challenges to NOTES

1.1.1. Experience

The NOTES main tool is a flexible scope and unstable working platform. Preliminary endoscopic, and to less degree laparoscopic, experience is a pre-request for conducting NOTES procedures. An excellent endoscopic experience is crucial in conducting NOTES procedures [8]. A study from Germany showed endoscopic experience was the strongest influencing factor, whereas laparoscopic skills had limited impact on the performance of NOTES surgeons with previous endoscopic experience [9]. This can be explained by the ability of the endoscopist to adapt for movement and to perform procedure using unstable and flexible platform. Reputable institutions are organising training courses for NOTES, and a good example is Strasbourg in France. Training on animal models is providing opportunity of operating on living subjects and increasing the confidence of performing the procedure on patients [10]. An example of the training model is the endoscopic–laparoscopic interdisciplinary training entity (ELITE) used in Germany. One of the important issues in training is the willingness and interest of the junior surgeons to adapt NOTES in their institutions.

1.1.2. Governance, regulations and training

Extensive training is required for surgeons to overcome the vision–motion difficulty before they can perform NOTES safely and effectively [11]. Different bodies are sponsoring NOTES training in the USA, Europe, South America and Asia. NOSCAR and EAES are leading the research, training and development of NOTES. In 2005, the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) formed the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) and published the NOTES white paper [12, 13]. In Europe, the New European Surgical Academy (NESA) founded the NOS (Natural Orifice Surgery) working group, which is exploring another surgical route, the TransDouglas (Td) one. The NOS/SLO group is an interdisciplinary working group of the NESA. Its goal is to develop surgical procedures using the natural openings of the human body and "scarless" operations [14]. There are similar scientific bodies in South America like Brazilian group and also in Asia like Japanese, Chinese and Indian NOTES groups. The Virtual Translumenal Endoscopic Surgical Trainer (VTEST (TM)) is being developed as a platform to train for NOTES procedures and innovate NOTES tools and techniques [15]. Different tools are used in NOTES training courses. These include operating on animal models with an acceptable grade of satisfaction. One of such tool is the endoscopic–laparoscopic interdisciplinary training entity. A study has shown the constructing validity for the ELITE model which seems to be well suited for the training of NOTES as a new surgical technique [16].

1.1.3. Funding

The rising costs of healthcare are forcing all parties to consider both the medical risks/benefits and the economic efficiency of proposed tools and therapies [17]. Funding is required for research and for setting of the infrastructure to perform NOTES procedures on animals and

patients. NOTES surgery needs extra cost for the instruments. The endoscopic closure devices, the working platforms and scope are very expensive compared to the classical laparoscopic instrumentations. Funding is a problem in the current era, and the leading teaching centres across America and Europe can afford it. The collaboration with businesses and industries has resulted in huge budget of funds to the NOTES research. For example, by 2009 Olympus has donated $1.25 million supporting NOTES activities in the USA [18]. Ethicon offered similar support and funding for NOSCAR research in the USA. The Center for Integration of Medicine and Innovative Technology's (CIMIT) investment in NOTES research will top $3 million overall, making CIMIT the largest financial sponsor of this technology worldwide [19].

1.1.4. Pressure of common acute and elective surgical take

Undertaking NOTES procedures in addition to the common surgical workload is adding a practical challenge. However, this can be resolved by dedicated time for specific NOTES activities. It is expected that NOTES will be a separate and distinguished speciality for the gastrointestinal surgeons.

1.1.5. Bureaucracy of health systems

It is not a surprise that the first reported NOTES procedure of appendicectomy was from the Hyderabad group in India which has less bureaucratic health system compared to Europe and the USA. The bureaucracy because of high grade of concerns about safety of any new technique or intervention. While this is a healthy issue, sometimes it defers innovations and frustrates surgeons who are trying to bring in reality and clinical practice new ideas and approaches. NOTES is not an exception to be rejected as a new method. In order to install NOTES technique, one would need extra efforts to pass through the hurdles that built up across modern health systems. In the UK we are much behind the fellow Europe states like Germany as far as NOTES is concerned. This may also be explained by less popularity of the technique in the UK. South London's Surrey University, Guildford, held the first ever NOTES training course in 2008. In the UK, there is no specific body to support NOTES research like NOSCAR in the USA or the NESA group of Europe.

1.1.6. Public opinion

As expected a study of 1006 patients demonstrated public's interest in these new techniques and thus gave further support to continued research and development in this area [20]. The Swanstrom group from the USA reported that majority of the patients surveyed (56%) would choose NOTES for their cholecystectomy [21]. It is not surprising that patients would choose an approach that provides excellent cosmetic and clinical outcomes with high safety profile [22]. Surgical societies are committed to work towards perfection, and NOTES is the ultimate approach for the management of a number of surgical conditions and provides extra benefits of minimal access techniques.

1.1.7. Septic complications

NOTES is not different from classical surgery of possible risk of infection. Intravenous antibiotics in addition to topical Betadine or chlorhexidine have effectively reduced microbial

http://dx.doi.org/10.5772/60552

burden in both gastric and colonic mucosa in porcine model [23]. The common Tg and Tv routes are compared in animal models, and authors concluded that without gastric or vaginal lavage and antibiotic peritoneal irrigation, the Tg procedure has a higher infection rate than the Tv access. After antiseptic preparation, the bacterial load significantly decreased in the Tg group, which seems as safe as the sterile Tv approach [24]. However, in a study of 40 patients who underwent Roux-En-Y gastric bypass (RYGBP), contamination of the peritoneal cavity does occur with Tg endoscopic peritoneoscopy (TEP), but this does not lead to an increased risk of infectious complications [25]. Another study of 130 patients who underwent Tg NOTES showed that the risk of bacterial contamination secondary to peroral and Tg access is clinically insignificant [26]. Pure Tg endoscopic surgery results in less perioperative inflammatory response than laparoscopy in the early postoperative phase [27]. In a review of literature by the Darzi group, UK showed that recommendation requiring no preoperative preparation can be made for the Tg approach. Antiseptic irrigation is recommended for Tv (grade C) NOTES access, as is current practice [28].

1.1.8. Intraoperative NOTES complications

The management of intraoperative NOTES complications could be challenging. Adequate experience is therefore necessary to recognise and treat them to avoid morbidity and mortality and to minimise conversion to hybrid NOTES or open technique. Effective management of NOTES complications however is reported, for example, bleeding complications and splenic laceration [29]. For intestinal perforation, the case may be different. Authors found that small intestinal injuries are difficult to localise with currently available flexible endoscopes and accessories. Endoscopic clips, however, may be adequate for closure of small bowel lacerations if the site of injury is known [30]. A study has shown that urinary bladder injury occurring during NOTES can be successfully managed via a NOTES approach using currently available endoscopic accessories [31].

1.2. Principles of NOTES

1.2.1. Indications

NOTES approach is indicated in a variety of conditions across surgical specialities, not only gastrointestinal tract but also urology, gynaecology and thoracic field. NOTES indications could be an emergency or elective which is the majority. This chapter is concentrating on upper GI NOTES.

1.2.2. Access

1.2.2.1. Major sites for access

1. Transgastric (Tg): The first human NOTES procedure was performed using Tg route. The experimental studies proved ultrasonography-guided access through the stomach to be feasible and safe without iatrogenic complications [32]. There are two challenges in the Tg route: the closure and the abdominal contamination and septic complications. The ideal

Tg access closure is expected to be easy, effective, cheap and less time consuming. Tg NOTES peritoneoscopy and the gastrotomy can be closed by deploying a 2-sided ECM occluder on animal model [33]. The results indicated that closure of gastrotomy by Eagle Claw VIII could withstand higher endoluminal pneumatic bursting pressure than endoclips [34]. Submucosal approach is a new and promising technique for the development of NOTES [35] (see Figure 1).

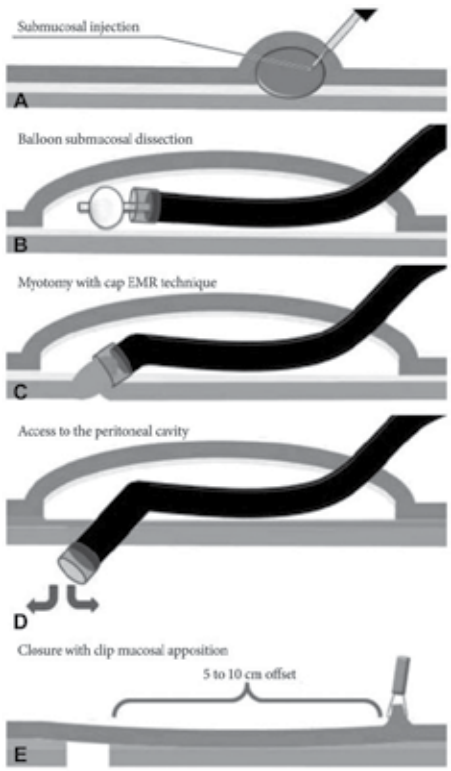

Figure 1. Submucosal tunnel technique is used (Lee SHI et al. 2012)

The Tg access closure is provided by different techniques including clips (over-the-scope clip), sutures, etc. [36, 37]. There are different closure methods in literature, but safety is shown in one of animal studies at least comparable to the classical laparoscopy procedure [38]. A novel gastric closure device, the loop-anchor purse-string (LAPS) closure system, had been described [39]. If hybrid technique is used, then laparoscopic stapler can be applied to the gastric access [40]. A multilayer extracellular matrix (ECM) occluder is assessed on animals, and it was safe and effective [41]. A loop and clip [KING closure], (see figure 2), [42] and QUEEN closure are other methods [43]. Self-approximating translumenal access technique (STAT) and implantation of a cellular matrix in the STAT tunnel are the two methods that have shown safety and efficacy on animal model [44]. There has been a method of testing support closure with T-tags and Padlock-G-clips over OVESCO OTS-clips and standard endoscopic clips [45].

http://dx.doi.org/10.5772/60552

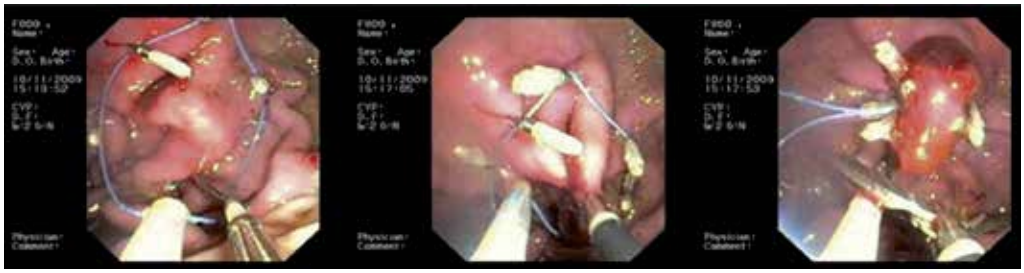

Figure 2. KING closure, loop and clip by Ryska O et al. 2012

2. Transvaginal (Tv): A recent meta-analysis confirmed high safety profile with this technique [46]. Infectious complications and the closure are the two important areas in this approach. A recent study of 102 Tv NOTES procedure reported only one case of infection following appendicectomy [47], which is comparable to the laparoscopic approach for similar pathology. Closure of the Tv access can be easier than Tg one [48]. Simple suturing under direct vision is the norm.

3. Transrectal (Tr): Animal studies have shown safety and efficacy [49]. The flexible endoscopic stapler is an effective device for the safe closure of a colon access, which in this feasibility study was equivalent to other well-established techniques [50]. Closure of Tr viscerotomy using end-to-end (EEA) circular stapler technique is feasible, easy to perform and histologically comparable to suture closure through a TEO platform. It may offer an attractive alternative for NOTES segmental colectomies and endoscopic resections [51]. The colostomy was closed by occlusion loop-and-clip (KING closure) technique [52]. To access the retroperitoneal space, significant challenges locating identifiable landmarks were faced mostly transrectally and improved in transgastric prone position [53].

4. Transvesical (Tve): Many animal studies have reported feasibility of NOTES procedures through the urinary bladder [54, 55]. Still there are no significant clinical applications on patients because of the challenging access closure and also because of the specimen delivery. J Bhullar et al. from Providence and medical centre, USA, used Vicryl loop for bladder access closure on a porcine model [56], (figure 3).

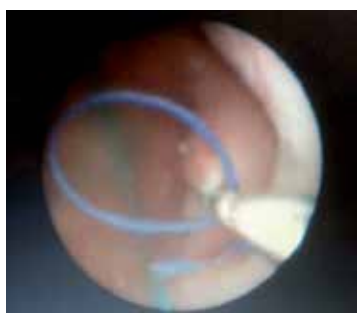

Figure 3. Vicryl loop closure of transvesical access (J Bhullar et al. 2012)

1.2.3. Instrumentation

Developing interfaces that are both intuitive and simple to use is crucial for NOTES dissemination [57]. The minimally invasive cardiac surgery (MICS) robot [58] is another step towards optimisation of the NOTES technique and to address the problems of optics, flexibility and the comfortable and adequate exposure. Abdominal navigation and accessing the pancreas was investigated on animals, and based on its success, pancreas resection was performed. A prototype multitasking platform "EndoSAMURAI" with the use of a biosimulation model and ex vivo porcine stomach was reported [59], (figure 5). There are new ancillary instruments like forceps, and training on using them is continuing [60]. The SPIDER platform is a sterile and disposable device that contains 4 working channels (2 flexible instrument delivery tubes positioned laterally and 2 rigid channels superiorly and inferiorly to accommodate an endoscope or any of the shelf rigid surgical instruments) [61]. This device has addressed some of the technical problems, and it is relatively expensive which limits its wide use. Authors concluded that the new manual handling system (MHS) is fully capable of achieving payload transport during a NOTES operation. The system is intuitive and easy to use. It dramatically decreases collateral trauma in the natural access point and can advantageously reduce the overall duration of a procedure [62]. The 3D display system is a great step in optics development. At least 34 systems are developed, for example, Aesculap's EinsteinVision (see Figure 4). This is in current use for laparoscopy and has the potential to improve the vision and anatomy at challenging NOTES procedures [63]. The Direct Drive Endoscopic System (DDES; Boston Scientific, Natick, MA) is a flexible laparoscopic multitasking platform that consists of a 55-cm steerable guide sheath that houses 3 lumens extending from a rail-based platform with interchangeable 4-mm instruments [64], (figure 6). Incisionless Operating Platform (IOP) is another flexible scope used for NOTES procedures including cholecystectomy [65].

Figure 4. Aesculap's EinsteinVision® system

1.2.4. Anaesthesia

There are three main issues when using transoral access to perform upper GI NOTES procedures: The first one is to intubate via transnasal route to spare the oral space for NOTES flexible scope, the second issue is to position the patient according to the type of procedure, and the

http://dx.doi.org/10.5772/60552

Figure 5. EndoSAMURAI platform, Yasuda K et al. 2014

Figure 6. Direct Drive Endoscopic System (DDES), S Shaik et al. 2010

third point is to monitor ETCO2 [66], (figure 7). For other NOTES accesses, transnasal intubation is not necessary. Anaesthetic technique can be different from laparoscopic surgery. The effect of pneumoperitoneum may be not different; both techniques will have pneumoperitoneum if it is abdominal NOTES procedure. POEM procedure, for example, does not need pneumoperitoneum [67, 68]. Any patient that cannot tolerate pneumoperitoneum because of cardiopulmonary disease is not a candidate for NOTES procedure. Cardiorespiratory physiology is affected by laparoscopic procedure mainly because of pneumoperitoneum. However, the non-inferiority of NOTES compared to the laparoscopy is demonstrated from reported studies, although the evidence is limited by a number of researches [69]. When administering anaesthetic care to a patient undergoing NOTES, anaesthesiologists should closely monitor the patient's position as well as ETCO2 to minimise the incidence of mediastinal emphysema and pneumomediastinum and to ensure early detection of pneumoperitoneum-related respiratory and hemodynamic changes [70].

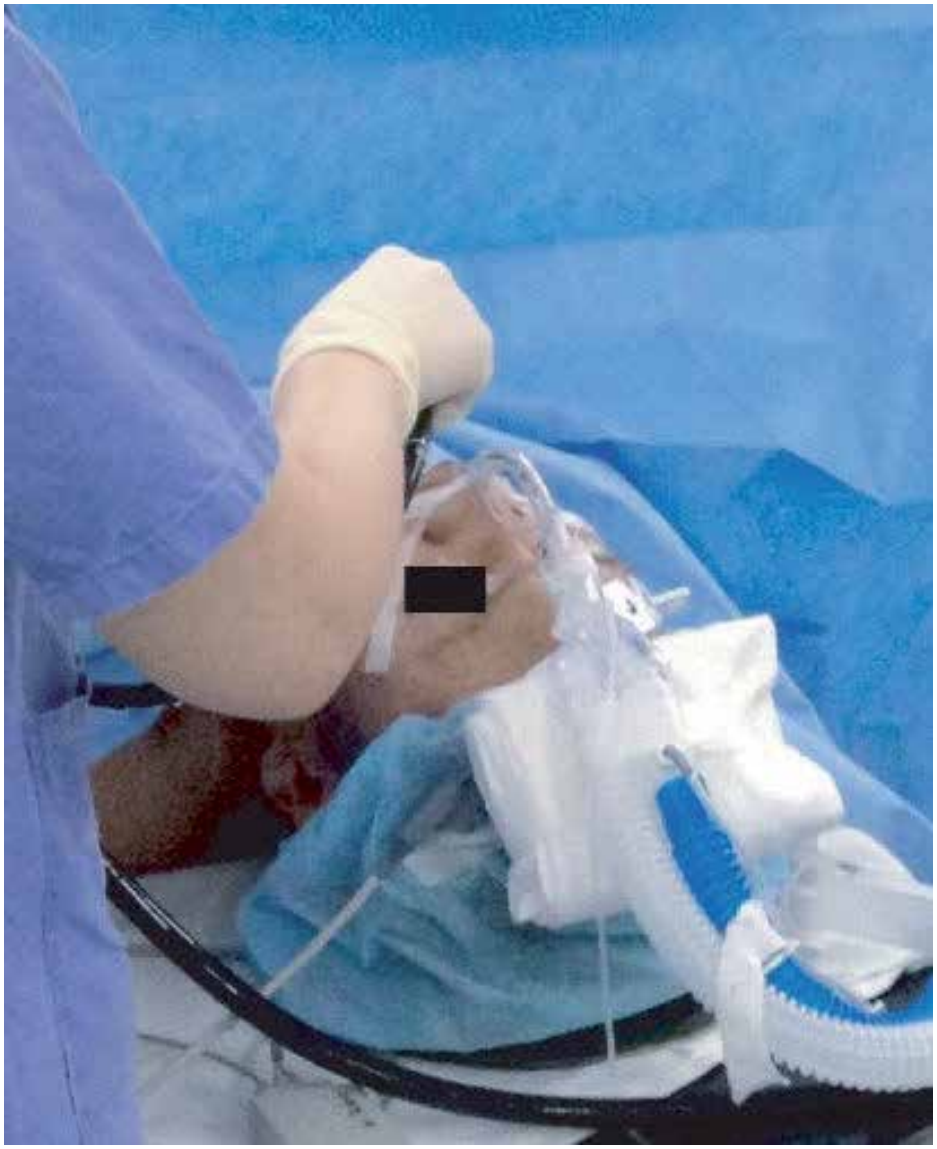

Figure 7. Transnasal intubation in upper GI NOTES. The patient was placed in the supine position and intubated via a nasal RAE™ tracheal tube. The endoscopic operator stood near the head of the patient and inserted the endoscope via the mouth (Ji Hyeon Lee et al. 2014)

1.2.5. Setting

NOTES units are part of surgical departments whether upper or lower GI, gynaecology and urology units. These units are usually located in well-established teaching hospitals. Theatre facilities are available for minimal access approach. Staffs are trained in NOTES, and they are familiar with the preparation and assistance.

http://dx.doi.org/10.5772/60552

1.2.6. Expertise

NOTES experience is crucial for the quality and safety of this intervention. The current guidelines advise to run through milestones of animal studies, cadaveric and live subject experimental and pilot projects. Once the learning curve is achieved after a number of procedures, NOTES can be performed under strict governance system. This has been achieved in a number of US and European states.

1.2.7. Complications

All minimal access surgery serious complications are those of organ injury due to suboptimal exposure that results from bad technique. It is anatomical and visual hallucination. This is to be avoided to provide the high grade of safety. Industries, related professionals and surgeons are striving to address all the issues that preclude safety.

2. Upper GI NOTES

2.1. Oesophagus NOTES

A number of oesophageal NOTES procedures are conducted safely on patients. Oesophageal discontinuity, which is a very complex procedure, is performed using a modification of NOTES [71]. The peroral endoscopic myotomy (POEM) for lower oesophageal conditions like achalasia has been performed on animals and patients with great success. NOSCAR has recently produced its white paper about the milestones of the POEM technique and the current opinion about the indications and quality and safety [72]. Distal oesophageal spasm that can progress to achalasia is another indication for POEM [73]. In 2002, Smith et al. found that the endoscopic stapling technique for the treatment of Zenker diverticulum results in a statistically significant shorter operative time, hospital stay and time to resume oral feedings compared with the standard open technique [74]. Transesophageal approach to posterior mediastinum has been reported on animal models [75]. Transoesophageal, anterior spinal NOTES reported lymph node resection, vagotomy, thoracic duct ligation, thymectomy, biopsy of the lung and pleura, epicardial coagulation, saline injection into the myocardium, pericardial fenestration and anterior thoracic spine procedures [76]. Exposure of the GOJ and placement of an anti-reflux prosthesis via a hybrid NOTES procedure were feasible, despite some complications [77]. Translumenal oesophago-oesophageal anastomosis was feasible on animal model [78]. Transoesophageal thoracic NOTES are a growing field. Diagnostic procedures have been well described. Closure of the oesophageal access is managed by different approaches including stenting [79].

2.2. Gastric NOTES

Gastric resection and specimen extraction through the upper GI route are reported by authors [80]. On animal models, a gastrojejunostomy was feasible with a 4-cm length using an anastomosing metal stent. After gastrotomy formation using a needle knife, a jejunotomy was

then performed in the gastric cavity, which was followed by deployment of an anastomosing metal stent under fluoroscopic guidance [81]. Also on porcine model, combined NOTES and single trocar sleeve gastrectomy is feasible in a porcine model [82]. Through Tv NOTES gastrectomy for gastric submucosal tumours, with the assistance of two transabdominal ports, "oncologically acceptable" partial gastrectomy was successfully performed [83].

The hybrid NOTES technique is a combined method, including the advantages of both laparoscopic resection and endoscopic resection for gastric subepithelial tumours (SETs) [84]. After a 40-mm submucosal tunnel was created using an endoscopic submucosal dissection technique, in TGP, balloon dilation of a serosal puncture and intraperitoneal exploration were performed; in EFTR, a full-thickness incision and snaring resection were performed. Closure of the mucosal incision was performed by endoclips [85].

Hybrid sleeve gastrectomy (SG) and delivery of the specimen by transoral remnant extraction (TORE) are feasible and avoid port complications [86]. A study of 136 patients showed that Tv hybrid NOTES SG technique can be performed, but there is still a need for additional trocars through the abdominal wall [87]. Combined use of laparoscopy and NOTES enabled gastric pull-up without cervical and thoracic incisions [88]. NOTES omental repair of gastric perforation appears comparable to that of laparoscopy [89]. Hybrid NOTES resection of gastric gastrointestinal stromal tumour (GIST) was successfully reported on patients [90].

2.3. Duodenal NOTES

Currently, there is scarce of literatures on duodenal NOTES. This is because of rarity of duodenal pathologies that benefits from NOTES. Peritoneoscopy is actively used to assess upper GI tract including the duodenum [91]. This approach is feasible in selected series of patients [92].

2.4. Liver NOTES

Continued development of NOTES techniques may further alter the approaches to the biliary tract, liver and pancreas [93]. On animal models intraoperative NOTES-EUS is feasible to assess liver lesions [94]. Liver biopsy was performed successfully without any bleeding, and adequate samples were obtained in animal cases [95]. Using the Erbe Jet2 water-jet system, transanal and transvaginal wedge hepatic resection was successfully performed [96]. Tr liver resection and delivery of specimen were feasible and safe without problem of the rectal access [97]. Another study reported an animal liver wedge resection using MASTER robot [98]. Human cases of liver resection were reported as well. A combined laparoscopic Tv approach was used. Four 5-mm trocars were used. The liver parenchyma was divided using the harmonic scalpel, whereas the left hepatic vein was transected using the laparoscopic Tv vascular stapler. The specimen was placed in an Endobag and extracted transvaginally [99]. Complex liver surgery like hepatico-jejunostomy, major hepatic resection and transplantation is unlikely to be introduced at this stage due to the current limitations of the technique.

http://dx.doi.org/10.5772/60552

2.5. Pancreas NOTES

It is technically possible by EUS-guided NOTES procedures to achieve a systematic anterior and posterior access for NOTES transgastric peritoneoscopy and direct pancreatic endoscopic procedures [100]. Peripancreatic abscess can be managed by transgastric endoscopy and debridement with successful outcome, which provides great benefits of minimal access approach [101, 102]. NOTES cystogastrostomy for pancreatic pseudocyst management included endoscopic ultrasound (EUS)-guided puncture of the stomach just below the gastroesophageal (GOJ) junction to gain access to the pseudocyst, guidewire placement and then dilatation with a balloon to 18–20 mm. Endoscopic necrosectomy and debridement were performed, followed by transoral surgical anastomosis under endoscopic visualisation with the SurgAssist™ SLC 55 (Power Medical Interventions, Langhorne, PA) using 4.8-mm stapler [103]. A robotic platform to perform complex distal pancreatectomy on animal model was described [104].

2.6. Spleen NOTES

To dissect the upper end of the gastrosplenic ligament and the marginal region between the left diaphragm and upper pole of the spleen, a flexible single-channel endoscope was introduced into the peritoneal cavity simultaneously with the use of a rigid laparoscope. This is also providing the benefits of water-jet lens cleaning, effective suction and better visualisation in dissection of all splenic attachments and ligaments [105]. Hybrid splenectomy is performed on animal models without major complications indicating safety and feasibility [106]. Tv visualisation of the spleen and standard dissection of attachments were feasible, and splenectomy was completed using Tv stapling of the splenic hilum which is safely performed on patient [107].

2.7. Biliary NOTES

A comparison of the surgical errors during electrosurgery gallbladder dissection establishes that the NOTES procedure, while still new, is not inferior to the established laparoscopic cholecystectomy procedure [108]. NOTES cholecystectomy is the commonest upper GI procedure performed on patients. More than 3000 procedures are reported by now. Largest series of more than 2653 cases is from Germany [109]. Only 15% of NOTES cholecystectomy is performed in the USA. Two recent review studies showed increasing number of NOTES cholecystectomy [110, 111]. NOTES peritoneoscopy for accurate diagnosis and staging of intra-abdominal cancers is already in clinical use. Peritoneoscopy can accurately assess hepato-pancreatic-biliary malignancy and lymph node status [112].

2.8. Bariatric Surgery NOTES

Authors reported combined Tv and abdominal variant of SG on humans [113]. On animal models, hybrid NOTES SG is reported [114, 115]. The procedure was performed on humans using hybrid technique [116]. Roux-En-Y GBP was very challenging procedure and needed development of NOTES instruments to make it safe, feasible and time-effective operation.

Trials on human cadavers concluded feasibility, but long operative time mainly because of the lack of proper instrumentation resulting in insufficient tissue traction, countertraction and instrument manipulation complicated several steps during the procedure [117]. There are human series of hybrid NOTES RYGBP for obesity [118]. NOTES gastric band procedure was reported on a patient [119].(see table 1).

Authors	Year	Reference	Operation	Human subjects	Animal subjects
Spaun GO et al.	2010	[134]	Transcervical Heller's myotomy	Yes	Yes
Swanstrom et al.	2010	[135]	Oesophageal mobilisation	Yes	Yes
Welhelm et al.	2010	[77]	Anti-reflux surgery	No	Yes
Swanstrom et al.	2011	[136,137,72]	Endoscopic myotomy	Yes	No
Rieder et al.	2011	[138,74]	Zenker diverticulectomy	No	Yes
Ishimaru et al.	2011	[139]	Gastric pull through for oesophageal atresia	No	Yes
Turner et al.	2011	[140]	Closure of oesophageal access site	No	Yes
Turners et al.	2011	[141,79]	Stent closure of oesophageal access site	No	Yes
Rolanda et al.	2011	[142]	Peroral oesophageal segmentectomy	No	Yes
Cho et al.	2011	[143]	Resection of early gastric cancer	Yes	No
Abe et al.	2009	[144]	Gastric submucosal tumour resection	Yes	No
Nau et al.	2011	[118]	Staging pancreatic mass	Yes	No
			Hybrid gastric bypass	Yes	No
			Pure gastric bypass	Yes	No
Chiu et al.	2010	[145]	Tg gastrojejunostomy	No	Yes
Campos et al.	2010	[146]	Tg drainage of abdominal abscess	Yes	No
Cahill et al.	2009	[147]	Tv gastric lymph node mapping	No	Yes
Luo et al.	2012	[148]	Tg gastrojejunostomy	No	Yes
Ikeda et al.	2011	[149]	Gastric full-thickness resection	No	Yes
Lacey et al.	2009	[150,112,87]	Hybrid sleeve gastrectomy	Yes	No
Michalik et al.	2011	[117]	Hybrid gastric band	Yes	No
Branco et al.	2011	[151]	Transvesical peritoneoscopy, liver biopsy, appendix manipulation	Yes	No
Truong et al.	2012	[152]	Hybrid liver resection	Yes	No
Shi et al.	2011	[153]	Pure liver resection	No	Yes
Lehman et al.	2014	[122]	Cholecystectomy	Yes	No

http://dx.doi.org/10.5772/60552

Authors	Year	Reference	Operation	Human subjects	Animal subjects
			Peritoneum	Yes	No
			Gastric surgery	Yes	No
			Liver surgery	Yes	No
Bakker OJ et al.	2012	[101,102]	Tg pancreatic necrosectomy	Yes	No
Pallapothu et al.	2011	[103]	Cystogastrostomy	Yes	No
Targarona et al.	2009	[107]	Tv splenectomy	Yes	No

Table 1. Important upper GI NOTES procedures

3. Lower GI NOTES

3.1. Small bowel NOTES

Small intestinal anastomosis was performed in a porcine intestinal Tr NOTES model using two robotic arms and a camera inserted through the proctoscope and a rectal anterior wall incision [120]. NOTES gastroenterostomy with a biflanged lumen-apposing stent was reported recently by collaboration of French and US centres. The procedure was feasible and safe with only one minor complication [121]. This has the potential to treat variable distal gastric pathology by this type of NOTES anastomosis.

3.2. Appendicectomy

The first human NOTES procedure was Tg appendicectomy performed by Rao and Reddy in 2004 in India. Many cases were reported after that [122, 123]. German registry showed that more than 6% [182 cases] of human NOTES procedure was appendicectomy done by Tg and Tv routes. Not only slim patients but also morbidly obese patients benefited from NOTES appendicectomy [124]. A 5-mm trocar was inserted through the umbilicus and a 5-mm telescope was placed. A 12-mm trocar and a 5-mm grasper were inserted separately through the posterior fornix of the vagina under laparoscopic guidance. The appendix was divided with an endoscopic stapler through the Tv 12-mm trocar and removed from the same trocar [125].

3.3. Colonic NOTES

Pure NOTES resection and anastomosis of the large bowel were feasible, and the colorectal anastomosis was achieved using circular stapler [126]. Early clinical series of transanal TME with laparoscopic assistance (n = 72) were promising, with overall intraoperative and postoperative complication rates of 8.3% and 27.8%, respectively, similar to laparoscopic TME [127]. NOTES TME was feasible and safe in this series of patients with mid- or low rectal tumours [128]. Transanal full-thickness circumferential rectal and mesorectal dissections were per-

formed, and a colorectal anastomosis was performed using a circular stapler with a single stapling technique. During the transanal approach, the gastrotomy was closed using four endoscopic clips [129]. On large series of human cadavers, transanal NOTES rectosigmoid resection with TME was feasible and demonstrates improvement in specimen length and operative time with experience. Transrectal retrograde rectosigmoid dissection was achieved in all attempts and showed numbers of lymph nodes similar to the laparoscopic group [130, 131]. A transrectal endoscopic device was used for optic assistance, colon dissection, ileum section and specimen retrieval. Transrectal MA-NOS total colectomy was assisted by three laparoscopic ports: A 12-mm port is used as the terminal ileostomy site [132]. Hybrid Tv resection of descending colon was feasible on animal model. Only one 5-mm transumbilical port was added for safety [133]. Long-segment Hirschsprung's disease was managed by NOTES. Authors reported the technique, which starts by a rectal mucosectomy 0.5 cm proximal to the dentate line and extending proximally to the level of the intraperitoneal rectum. Three cannulas were inserted through the muscular sleeve into the abdominal cavity. After colonic mobilisation, the ganglionic distal bowel segment was pulled through the anus and resected and the colo-anal anastomosis was created [134], (see table 2).

Authors	Year	Reference	Operation	Human subjects	Animal subjects
Demura et al.	2013	[119]	Small bowel anastomosis	No	Yes
Barthet M et al.	2015	[120]	Gastroenterostomy	Yes	No
Lehman et al.	2014	[122]	Appendicectomy	Yes	No
Bernhardt J et al.	2012	[125]	Sigmoid colectomy	No	Yes
Chouillard et al.	2014	[127]	TME	Yes	No
Park SJ et al.	2013	[128]	Rectosigmoid resection	No	Yes
Telem DA et al.	2013	[129]	TME [cadavers]	Yes	No
Lacy AM et al.	2012	[131]	Hybrid total colectomy	Yes	No
Alba mesa et al.	2012	[132]	Descending colon resection	No	Yes
Li N et al.	2013	[133]	Hirschsprung's segment resection	Yes	No

Table 2. Important lower GI NOTES procedures

4. Further research

NOTES is evolving and refinement of the technique is warranted for feasibility, safety, operative time effectiveness and practicality. Three hot areas are expected to be the focus for further research:

1. Development of technology: this includes instruments, optics and working platforms.

http://dx.doi.org/10.5772/60552

2. Exploration of practicality of NOTES application in complex abdominal procedures and new fields like thoracic and retroperitoneal procedures.

3. Training: NOTES needs an advanced endoscopic and minimal access skills. Surgeons who already attended this level are those who are leading NOTES research in the respected academic institutions in the USA, Europe and Asia. What is needed is to organise an effective and specific dedicated training programme to produce NOTES trained surgeons. NOTES is expected to be an independent specialty that works to meet patient's expectation by making the most use of modern surgery and technology.

5. Conclusions

NOTES is gaining interest and popularity among surgeons. Many new procedures are reported as feasibility studies on animal models. Other procedures are starting to establish itself in clinical practice like NOTES cholecystectomy, appendicectomy and peritoneoscopy. Tv and Tg access routes are the commonest and closure technique is evolving to achieve a high degree of safety and effectiveness. Many new clinical procedures are introduced and currently are at experimental level. Development of the technology and instrumentation, effective training and support are expected to push NOTES further towards its long track of refinement and milestone journey towards an accepted and well-established standard technique.

Author details

Abdulzahra Hussain[1,2*]

Address all correspondence to: abdulzahra.hussain@nhs.net

1 Upper GI Surgeon at Airedale Hospital NHS Foundation Trust, Keighley, Bradford, UK

2 Honorary Senior Lecturer, King's College Medical School, London, UK

References

[1] Lau WY, Leow CK, Li AK. History of endoscopic and laparoscopic surgery. World J Surg. 1997;21(4):444-453.

[2] José FN. and Angel C.. NOTES, MANOS, SILS and other new laparoendoscopic techniques.World J Gastrointest Endosc. 2012; 4(6): 212-7.

[3] Hatzinger M1, Fesenko A, Sohn M. The first human laparoscopy and NOTES operation: Dimitrij Oscarovic Ott (1855-1929).Urol Int. 2014;92(4):387-91.

[4] http://www.baus.org.uk/Resources/BAUS/Documents/10-hopkins.pdf. Date of access 13/11/2014.

[5] Kalloo AN1, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, Magee CA, Kantsevoy SV. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastrointest Endosc. 2004 ; 60(1):114-7.

[6] Hussain A, Mahmood H. NOTES: current status and expectations. European Surgery.2008; 40(4);176-186.

[7] Von Renteln D1, Gutmann TE, Schmidt A, Vassiliou MC, Rudolph HU, Caca K. Standard diagnostic laparoscopy is superior to NOTES approaches: results of a blinded randomized controlled porcine study. Endoscopy. 2012;44(6):596-604.

[8] Auyang ED, Santos BF, Enter DH, Hungness ES, Soper NJ.Natural orifice translumenal endoscopic surgery (NOTES(®)): a technical review.Surg Endosc. 2011;25(10): 3135-48

[9] Gillen S1, Gröne J, Knödgen F, Wolf P, Meyer M, Friess H, Buhr HJ, Ritz JP, Feussner H, Lehmann KS. Educational and training aspects of new surgical techniques: experience with the endoscopic–laparoscopic interdisciplinary training entity (ELITE) model in training for a natural orifice translumenal endoscopic surgery (NOTES) approach to appendectomy. Surg Endosc. 2012;26(8):2376-82.

[10] Song S, Itawi EA, Saber AA. Natural orifice translumenal endoscopic surgery (NOTES). J Invest Surg. 2009;22(3):214-7.

[11] Cassera MA1, Zheng B, Spaun GO, Swanström LL. Optimizing surgical approach for natural orifice translumenal endoscopic procedures. Surg Innov. 2012;19(4):433-7.

[12] Rattner D, Kalloo AN, The SAGES/ASGE working group on natural orifice translumenal endoscopic surgery ASGE/SAGES working group on natural orifice translumenal endoscopic surgery. Surg Endosc. 2005;20(2):329–33.

[13] Rattner D. Introduction to NOTES white paper. Surg Endosc. 2006;20(2):185.

[14] http://www.nesacademy.org/projects.html. Date of access 03/12/2014.

[15] Dargar S1, Solley T, Nemani A, Brino C, Sankaranarayanan G, De S. The development of a haptic interface for the Virtual Translumenal Endoscopic Surgical Trainer (VTEST). Stud Health Technol Inform. 2013;184:106-8.

[16] Gillen S, Fiolka A, Kranzfelder M, Wolf P, Feith M, Schneider A, Meining A, Friess H, Feussner H.Training of a standardized natural orifice transluminal endoscopic surgery cholecystectomy using an ex vivo training unit. Endoscopy. 2011;43(10): 876-81.

[17] Schwaitzberg SD1, Hawes RH, Rattner DW, Kochman ML. Novel challenges of multi-society investigator-initiated studies: a paradigm shift for technique and technology evaluation. Surg Endosc. 2013;27(8):2673-7.

[18] http://www.endonurse.com/news/2009/07/olympus-donates-250-000-to-notes-research.aspx. Date of access 03/12/2014.

[19] http://www.cimit.org/programs-notes.html. Date of access 25/12/2014.

[20] Chow A1, Purkayastha S, Dosanjh D, Sarvanandan R, Ahmed I, Paraskeva P. Patient reported outcomes and their importance in the development of novel surgical techniques. Surg Innov. 2012;19(3):327-34.

[21] Swanstrom LL1, Volckmann E, Hungness E, Soper NJ. Patient attitudes and expectations regarding natural orifice translumenal endoscopic surgery. Surg Endosc. 2009;23(7):1519-25.

[22] Fei YF, Fei L, Salazar M, Renton DB, Hazey JW. Transvaginal surgery: do women want it. J Laparoendosc Adv Surg Tech A. 2014;24(10):676-83.

[23] Ryou M1, Hazan R, Rahme L, Thompson CC. An ex vivo bacteriologic study comparing antiseptic techniques for natural orifice translumenal endoscopic surgery (NOTES) via the gastrointestinal tract. Dig Dis Sci. 2012;57(8):2130-6.

[24] Yang QY1, Zhang GY, Wang L, Wang ZG, Li F, Li YQ, Ding XJ, Hu SY. Infection during transgastric and transvaginal natural orifice transluminal endoscopic surgery in a live porcine model. Chin Med J (Engl). 2011;124(4):556-61.

[25] Memark VC1, Anderson JB, Nau PN, Shah N, Needleman BJ, Mikami DJ, Melvin WS, Hazey JW. Transgastric endoscopic peritoneoscopy does not lead to increased risk of infectious complications. Surg Endosc. 2011;25(7):2186-91.

[26] Nau P1, Ellison EC, Muscarella P Jr, Mikami D, Narula VK, Needleman B, Melvin WS, Hazey JW. A review of 130 humans enrolled in transgastric NOTES protocols at a single institution. Surg Endosc. 2011;25(4):1004-11.

[27] Georgescu I1, Saftoiu A, Patrascu S, Silosi I, Georgescu E, Surlin V. Perioperative inflammatory response in natural orifice translumenal endoscopic surgery. Surg Endosc. 2013;27(7):2551-6.

[28] Sodergren MH1, Pucher P, Clark J, James DR, Sockett J, Matar N, Teare J, Yang GZ, Darzi A. Disinfection of the access orifice in NOTES: evaluation of the evidence base. Diagn Ther Endosc. 2011;(2011):245175. doi: 10.1155/2011/245175.

[29] Fyock CJ1, Kowalczyk LM, Gupte AR, Forsmark CE, Wagh MS. Complications during natural orifice translumenal endoscopic surgery: endoscopic management of splenic laceration and hemorrhage. J Laparoendosc Adv Surg Tech A. 2011;21(1): 39-43.

[30] Fyock CJ1, Forsmark CE, Wagh MS. Endoscopic management of intraoperative small bowel laceration during natural orifice translumenal endoscopic surgery: a blinded porcine study. Surg Tech A. 2011;21(6):525-30.

[31] Fyock CJ1, Parekattil SJ, Atalah H, Su LM, Forsmark CE, Wagh MS. The NOTES approach to management of urinary bladder injury. JSLS. 2011;15(3):285-90.

[32] Donatsky AM. Assessing transgastric natural orifice transluminal endoscopic surgery prior to clinical implementation. Dan Med J. 2014;61(8):B4903.

[33] Sanz AF1, Hoppo T, Witteman BP, Brown BN, Gilbert TW, Badylak SF, Jobe BA, Nieponice A. In vivo assessment of a biological occluder for NOTES gastrotomy closure. Surg Laparosc Endosc Percutan Tech. 2014;24(4):322-6.

[34] Liu L1, Chiu PW, Teoh AY, Lam CC, Ng EK, Lau JY. Endoscopic suturing is superior to endoclips for closure of gastrotomy after natural orifices translumenal endoscopic surgery (NOTES): an ex vivo study. Surg Endosc. 2014 ;28(4):1342-7.

[35] Lee SH1, Cho WY, Cho JY. Submucosal endoscopy, a new era of pure natural orifice translumenal endoscopic surgery (NOTES).Clin Endosc. 2012;45(1):4-10.

[36] Sanz AF, Hoppo T, Witteman BP, Brown BN, Gilbert TW, Badylak SF, Jobe BA, Nieponice A. In vivo assessment of a biological occluder for NOTES gastrotomy closure. Surg Laparosc Endosc Percutan Tech. 2014;24(4):322-6.

[37] Sun G, Yang Y, Zhang X, Li W, Wang Y, Zhang L, Tang P, Kong J, Zhang R, Meng J, Wang X. Comparison of gastrotomy closure modalities for natural orifice transluminal surgery: a canine study. Gastrointest Endosc. 2013;77(5):774-83.

[38] Guarner-Argente C1, Beltrán M, Martínez-Pallí G, Navarro-Ripoll R, Martínez-Zamora MÀ, Córdova H, Comas J, De Miguel CR, Rodríguez-D'Jesús A, Almela M, Hernández-Cera C, Lacy AM, Fernández-Esparrach G. Infection during natural orifice transluminal endoscopic surgery peritoneoscopy: a randomized comparative study in a survival porcine model. J Minim Invasive Gynecol. 2011;18(6):741-6.

[39] Romanelli JR1, Desilets DJ, Chapman CN, Surti VC, Lovewell C, Earle DB. Loop-anchor purse-string closure of gastrotomy in NOTES(R) procedures: survival studies in a porcine model. Surg Innov. 2010;17(4):312-7.

[40] Dostalik J, Gunkova P, Gunka I, Mazur M, Mrazek T. Laparoscopic gastric resection with natural orifice specimen extraction for postulcer pyloric stenosis.Wideochir Inne Tech Malo Inwazyjne. 2014; 9(2): 282–285.

[41] Sanz AF1, Hoppo T, Witteman BP, Brown BN, Gilbert TW, Badylak SF, Jobe BA, Nieponice A. In vivo assessment of a biological occluder for NOTES gastrotomy closure. Surg Laparosc Endosc Percutan Tech. 2014;24(4):322-6.

[42] Ryska O, Martinek J, Filipkova T, Dolezel R, Juhasova J, Motlik J, Zavoral M, Ryska M. Single loop-and-clips technique (KING closure) for gastrotomy closure after

transgastric ovariectomy: a survival experiment. Wideochir Inne Tech Malo Inwazyjne. 2012 ;7(4):233-9.

[43] Hookey LC, Khokhotva V, Bielawska B, et al. The Queen's closure: a novel technique for closure of endoscopic gastrotomy for natural-orifice transluminal endoscopic surgery. Endoscopy. 2009;41(2):149–53.

[44] Gopal J1, Pauli EM, Haluck RS, Moyer MT, Mathew A. Intramural acellular porcine dermal matrix (APDM)-assisted gastrotomy closure for natural orifice transluminal endoscopic surgery (NOTES). Surg Endosc. 2012;26(8):2322-30.

[45] Azadani A1, Bergström M, Dot J, Abu-Suboh-Abadia M, Armengol-Miró JR, Park PO. A new in vivo method for testing closures of gastric NOTES incisions using leak of the closure or gastric yield as endpoints. J Laparoendosc Adv Surg Tech A. 2012 ; 22(1):46-50.

[46] Sodergren MH1, Markar S, Pucher PH, Badran IA, Jiao LR, Darzi A. Safety of transvaginal hybrid NOTES cholecystectomy: a systematic review and meta-analysis. Surg Endosc. 2014; (26) [Epub ahead of print].

[47] Wood SG1, Panait L, Duffy AJ, Bell RL, Roberts KE. Complications of transvaginal natural orifice transluminal endoscopic surgery: a series of 102 patients. Ann Surg. 2014;259(4):744-9.

[48] Zornig C1, Mofid H, Siemssen L, Wenck CH. Transvaginal access for NOTES. Chirurg. 2010;81(5):426-30.

[49] Kono Y1, Yasuda K, Hiroishi K, Akagi T, Kawaguchi K, Suzuki K, Yoshizumi F, Inomata M, Shiraishi N, Kitano S. Transrectal peritoneal access with the submucosal tunnel technique in NOTES: a porcine survival study. Surg Endosc. 2013;27(1):278-85.

[50] Sodergren M1, Clark J, Beardsley J, Bryant T, Horton K, Darzi A, Teare J. A novel flexible endoluminal stapling device for use in NOTES colotomy closure: a feasibility study using an ex vivo porcine model. Surg Endosc. 2011;25(10):3266-72.

[51] Diana M1, Leroy J, Wall J, De Ruijter V, Lindner V, Dhumane P, Mutter D, Marescaux J. Prospective experimental study of transrectal viscerotomy closure using transanal endoscopic suture vs. circular stapler: a step toward NOTES. Endoscopy. 2012 ;44(6):605-11.

[52] Ryska O1, Filípková T, Martínek J, Dolezel R, Juhás S, Juhásová J, Zavoral M, Ryska M. [Transrectal hybrid NOTES versus laparoscopic cholecystectomy--a randomized prospective study in a large laboratory animal] Rozhl Chir. 2011;90(12):695-700.

[53] Moran EA1, Bingener J, Murad F, Levy MJ, Gostout CJ. The challenges with NOTES retroperitoneal access in humans. Surg Endosc. 2011;25(4):1096-100.

[54] Bin X1, Bo Y, Dan S, Okhunov Z, Ghiraldi E, Huiqing W, Friedlander J, Liang X, Yinghao S, Kavoussi LR. A novel transvesical port for natural orifice translumenal endoscopic surgery. J Endourol. 2012;26(3):219-23.

[55] Jeong CW1, Oh JJ, Abdullajanov M, Yeon J, Lee HE, Jeong SJ, Hong SK, Byun SS, Lee SB, Kim HH, Lee SE. Pure transvesical NOTES uterine horn resection in swine as an appendectomy model. Surg Endosc. 2012;26(2):558-64.

[56] Bhullar JS, Subhas G, Gupta A, Jacobs MJ, Decker M, Silberberg B, Mittal VK. Transvesical NOTES: survival study in porcine model. JSLS. 2012;16(4):606-11.

[57] Kranzfelder M1, Schneider A2, Fiolka A2, Koller S2, Wilhelm D2, Reiser S2, Meining A2, Feussner H2. What do we really need? Visions of an ideal human-machine interface for NOTES mechatronic support systems from the view of surgeons, gastroenterologists, and medical engineers. Surg Innov. 2014;(23). pii: 1553350614550720. [Epub ahead of print].

[58] Thakkar S1, Awad M2, Gurram KC3, Tully S4, Wright C4, Sanan S4, Choset H4. A novel, new robotic platform for natural orifice distal pancreatectomy. Surg Innov. 2014(15). pii: 1553350614554232. [Epub ahead of print].

[59] Yasuda K, Kitano S, Ikeda K, Sumiyama K, Tajiri H. Assessment of a manipulator device for NOTES with basic surgical skill tests: a bench study. Surg Laparosc Endosc Percutan Tech. 2014;24(5):e191-5.

[60] Addis M1, Aguirre M, Frecker M, Haluck R, Matthew A, Pauli E, Gopal J. Development of tasks and evaluation of a prototype forceps for NOTES. JSLS. 2012;16(1): 95-104.

[61] Villamizar N1, Pryor AD. SPIDER and flexible laparoscopy: the next frontier in abdominal surgery. Surg Technol Int. 2010 ;20:53-8.

[62] Midday J1, Nelson CA, Oleynikov D. Improvements in robotic natural orifice surgery with a novel material handling system. Surg Endosc. 2013;27(9):3474-7.

[63] http://www.bbraun.com. Date of access 21/12/2014.

[64] Sohail N Shaikh and Christopher C Thompson. Natural orifice translumenal surgery: Flexible platform review.World J Gastrointest Surg. 2010;27; 2(6): 210-6.

[65] Swanström L, Swain P, Denk P. Development and validation of a new generation of flexible endoscope for NOTES. Surg Innov. 2009;(16):104-10.

[66] Ji Hyeon Lee, Chan Jong Chung, Seung Cheo Lee, Ho Jin Shin. Anesthetic management of transoral natural orifice transluminal endoscopic surgery: two cases report. Korean J Anesthesiol. 2014;67(2):148-52.

[67] Schaefer M. Natural orifice transluminal endoscopic surgery (NOTES): implications for anesthesia. F1000 Med Rep. 2009;1:80. doi: 10.3410/M1-80.

[68] Phalanusitthepha C, Inoue H, Ikeda H, Sato H, Sato C, Hokierti C. Peroral endoscopic myotomy for esophageal achalasia. Ann Transl Med. 2014;2(3):31.

[69] Grabowski JE, Talamini MA. Physiological effects of pneumoperitoneum. J Gastro intest Surg. 2009;13(5):1009-16.

[70] Pucher P1, Sodergren MH, Alkhusheh M, Clark J, Jethwa P, Teare J, Yang GZ, Darzi A. The effects of natural orifice translumenal endoscopic surgery (NOTES) on cardiorespiratory physiology: a systematic review. Surg Innov. 2013;20(2):183-9.

[71] Chang ET1, Ruhl DS, Kenny PR, Sniezek JC. Endoscopic management of esophageal discontinuity. Head Neck. 2014;(1). doi: 10.1002/hed.23883 [Epub ahead of print].

[72] Modayil R, Savides T, Scott DJ, Swanstrom LL, Vassiliou MC. Per-oral endoscopic myotomy white paper summary. NOSCAR POEM White Paper Committee, Stavropoulos SN, Desilets DJ, Fuchs KH, Gostout CJ, Haber G, Inoue H, Kochman ML, Gastrointest Endosc. 2014;80(1):1-15.

[73] Achem SR1, Gerson LB. Distal esophageal spasm: an update. Curr Gastroenterol Rep. 2013;15(9):325.

[74] Smith SR1, Genden EM, Urken ML. Endoscopic stapling technique for the treatment of Zenker diverticulum vs standard open-neck technique: a direct comparison and charge analysis. Arch Otolaryngol Head Neck Surg. 2002;128(2):141-4.

[75] Woodward TA, Jamil LH, Wallace MB. Natural orifice trans-luminal endoscopic surgery in the esophagus. Gastrointestinal Endoscopy Clinics of North America. 2010;20(1):123-138.

[76] Magno p, Khashab MA, Mas M, Giday SA, Buscaglia JA, Shin EJ, Dray X, and Kalloo AN. Natural orifice translumenal endoscopic surgery for anterior spinal procedures. Minim Invasive Surg. 2012;2012: 365814. doi: 10.1155/2012/365814.

[77] Wilhelm D1, Meining A, Schneider A, Von Delius S, Preissel A, Sager J, Fiolka A, Friess H, Feussner H. NOTES for the cardia: antireflux therapy via transluminal access. Endoscopy. 2010;42(12):1085-91.

[78] Ishimaru T1, Iwanaka T, Hatanaka A, Kawashima H, Terawaki K. Translumenal esophageal anastomosis for natural orifice translumenal endoscopic surgery: an ex vivo feasibility study. J Laparoendosc Adv Surg Tech A. 2012;22(7):724-9.

[79] Brian G Turner, Denise W Gee. Natural orifice transesophageal thoracoscopic surgery: A review of the current state. World J Gastrointest Endosc. 2010; 2(1):3-9.

[80] Dostalik J1, Gunkova P2, Gunka I3, Mazur M2, Mrazek T1. Laparoscopic gastric resection with natural orifice specimen extraction for postulcer pyloric stenosis. Wideochir Inne Tech Malo Inwazyjne. 2014;9(2):282-5.

[81] Yi SW1, Chung MJ, Jo JH, Lee KJ, Park JY, Bang S, Park SW, Song SY. Gastrojejunostomy by pure natural orifice transluminal endoscopic surgery using a newly de-

signed anastomosing metal stent in a porcine model. Surg Endosc. 2014;28(5): 1439-46.

[82] Elazary R1, Schlager A2, Khalaileh A2, Mintz Y2. Laparoscopic sleeve gastrectomy with transgastric visualization: another step toward totally NOTES procedures. Surg Innov. 2014;21(5):464-8.

[83] Nakajima K1, Takahashi T1, Yamasaki M1, Kurokawa Y1, Miyazaki Y1, Miyata H1, Takiguchi S1, Mori M1, Doki Y1. [Transvaginal natural orifice translumenal endoscopic surgery partial gastrectomy: initial clinical experience] Nihon Geka Gakkai Zasshi. 2013;114(6):303-7.

[84] Heo J1, Jeon SW. Hybrid natural orifice transluminal endoscopic surgery in gastric subepithelial tumors. World J Gastrointest Endosc. 2013;16;5(9):428-32.

[85] Lee SH1, Kim SJ, Lee TH, Chung IK, Park SH, Kim EO, Lee HJ, Cho HD. Human applications of submucosal endoscopy under conscious sedation for pure natural orifice transluminal endoscopic surgery. Surg Endosc. 2013;27(8):3016-20.

[86] Dotai T1, Coker AM, Antozzi L, Acosta G, Michelotti M, Bildzukewicz N, Sandler BJ, Jacobsen GR, Talamini MA, Horgan S. Transgastric large-organ extraction: the initial human experience. Surg Endosc. 2013;27(2):394-9.

[87] Buesing M1, Utech M, Halter J, Riege R, Saada G, Knapp A. [Sleeve gastrectomy in the treatment of morbid obesity. Study results and first experiences with the transvaginal hybrid NOTES technique] Chirurg. 2011;82(8):675-83.

[88] Ishimaru T1, Iwanaka T, Kawashima H, Terawaki K, Kodaka T, Suzuki K, Takahashi M. A pilot study of laparoscopic gastric pull-up by using the natural orifice translumenal endoscopic surgery technique: a novel procedure for treating long-gap esophageal atresia (type a). J Laparoendosc Adv Surg Tech A. 2011;21(9):851-7.

[89] Moran EA1, Gostout CJ, McConico AL, Michalek J, Huebner M, Bingener J. Assessing the invasiveness of NOTES perforated viscus repair: a comparative study of NOTES and laparoscopy. Surg Endosc. 2012;26(1):103-9.

[90] Mori H1, Kobara H, Kobayashi M, Muramatsu A, Nomura T, Hagiike M, Izuishi K, Suzuki Y, Masaki T. Establishment of pure NOTES procedure using a conventional flexible endoscope: review of six cases of gastric gastrointestinal stromal tumors. Endoscopy. 2011;43(7):631-4.

[91] Alford C, Hanson R. Evaluation of a transvaginal laparoscopic natural orifice transluminal endoscopic surgery approach to the abdomen of mares. Vet Surg. 2010;39(7): 873-8.

[92] Hyder Q1, Zahid MA, Ahmad W, Rashid R, Hadi SF, Qazi S, Haider HK. Diagnostic transgastric flexible peritoneoscopy: is pure natural orifice transluminal endoscopic surgery a fantasy? Singapore Med J. 2008;49(12):e375-81.

[93] Potter K1, Swanstrom L. Natural orifice surgery (NOTES) and biliary disease, is there a role? J Hepatobiliary Pancreat Surg. 2009;16(3): 261-5.

[94] Fyock CJ, Kirtane TS, Forsmark CE, Wagh MS. Intraoperative NOTES endosonography and identification of mock hepatic lesions. Surg Laparosc Endosc Percutan Tech. 2012;22(1):e1-4.

[95] Tagaya N1, Kubota K. NOTES: approach to the liver and spleen. J Hepatobiliary Pancreat Surg. 2009;16(3):283-7.

[96] Shi H1, Jiang SJ, Li B, Fu DK, Xin P, Wang YG. Natural orifice transluminal endoscopic wedge hepatic resection with a water-jet hybrid knife in a non-survival porcine model. World J Gastroenterol. 2011;17(7):926-31.

[97] Ohdaira T1, Endo K, Abe N, Yasuda Y. Transintestinal hepatectomy performed by hybrid NOTES using a customized X-TRACT Tissue Morcellator with an electrifiable round cutter. J Hepatobiliary Pancreat Surg. 2009;16(3):274-82.

[98] Phee SJ1, Ho KY, Lomanto D, Low SC, Huynh VA, Kencana AP, Yang K, Sun ZL, Chung SC. Natural orifice transgastric endoscopic wedge hepatic resection in an experimental model using an intuitively controlled master and slave transluminal endoscopic robot (MASTER). Surg Endosc. 2010;24(9):2293-8.

[99] Truong T1, Arnaoutakis D, Awad ZT. Laparoscopic hybrid NOTES liver resection for metastatic colorectal cancer. Surg Laparosc Endosc Percutan Tech. 2012;22(1):e5-7.

[100] Saftoiu A1, Bhutani MS, Vilmann P, Surlin V, Uthamanthil RK, Lee JH, Bektas M, Singh H, lonut D, Gheonea, Pactrascu S, Gupta V, Katz MH, Fleming JB. Feasibility study of EUS-NOTES as a novel approach for pancreatic cancer staging and therapy: an international collaborative study. Hepatogastroenterology. 2013;60(121):180-6.

[101] Wang XW, Fan CQ, Wang L, Guo H, Xie X, Zhao GC, Zhao XY. Transoralgastric gastroscopic debridement for peripancreatic abscess: a special case report. Hepatogastroenterology. 2011;58(110-111):1801-4.

[102] Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. Bakker OJ, Van Santvoort HC, Van Brunschot S, Geskus RB, Besselink MG, Bollen TL, Van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, Van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R; Dutch Pancreatitis Study Group.JAMA. 2012;07(10):1053-61.

[103] Pallapothu R1, Earle DB, Desilets DJ, Romanelli JR. NOTES(®) stapled cystgastrostomy: a novel approach for surgical management of pancreatic pseudocysts. Surg Endosc. 2011;25(3):883-9.

[104] Thakkar S, Awad M, Gurram KC, Tully S, Wright C, Sanan S, Choset H. A novel, new robotic platform for natural orifice distal pancreatectomy. Surg Innov. 2014;(15). pii: 1553350614554232 [Epub ahead of print].

[105] Tomikawa M1, Akahoshi T, Kinjo N, Uehara H, Hashimoto N, Nagao Y, Kamori M, Kumashiro R, Maehara Y, Hashizume M. Rigid and flexible endoscopic rendezvous in spatium peritonealis may be an effective tactic for laparoscopic megasplenectomy: significant implications for pure natural orifice translumenal endoscopic surgery. Surg Endosc. 2012; 26(12): 3573-9.

[106] Tagaya N1, Kubota K. NOTES: approach to the liver and spleen. J Hepatobiliary Pancreat Surg. 2009;16(3):283-7.

[107] Targarona EM, Gomez C, Rovira R, Pernas JC, Balague C, Guarner-Argente C, Sainz S, Trias M. NOTES-assisted transvaginal splenectomy: the next step in the minimally invasive approach to the spleen. Surg Innov. 2009;16(3):218-22.

[108] Nemani A1, Sankaranarayanan G, Olasky JS, Adra S, Roberts KE, Panait L, Schwaitzberg SD, Jones DB, De S. A comparison of NOTES transvaginal and laparoscopic cholecystectomy procedures based upon task analysis. Surg Endosc. 2014;28(8): 2443-51.

[109] Lehmann KS1, Zornig C, Arlt G, Butters M, Bulian DR, Manger R, Burghardt J, Runkel N, Pürschel A, Köninger J, Buhr HJ. [Natural orifice transluminal endoscopic surgery in Germany : Data from the German NOTES registry.] Chirurg. 2014; (5) [Epub ahead of print].

[110] A Hussain. Upper GI natural orifice translumenal endoscopic surgery: what is new? European Surgery. 2014; 46(1): 3-11.

[111] Sodergren MH1, Markar S, Pucher PH, Badran IA, Jiao LR, Darzi A. Safety of transvaginal hybrid NOTES cholecystectomy: a systematic review and meta-analysis. Surg Endosc. 2014;26 [Epub ahead of print].

[112] Yasuda K1, Kitano S. Lymph node navigation for pancreatic and biliary malignancy by NOTES. J Hepatobiliary Pancreat Sci. 2010;17(5):617-21.

[113] Chouillard EK1, Al Khoury M, Bader G, Heitz D, Elrassi Z, Fauconnier A. Intercontinental Society of Natural Orifice, Endoscopic, Laparoscopic Surgery (i-NOELS), Poissy, France. Combined vaginal and abdominal approach to sleeve gastrectomy for morbid obesity in women: a preliminary experience. Surg Obes Relat Dis. 2011;7(5): 581-6.

[114] Elazary R, Schlager A, Khalaileh A, Mintz Y. Laparoscopic sleeve gastrectomy with transgastric visualization: another step toward totally NOTES procedures. Surg Innov. 2014;21(5):464-8.

[115] Mintz Y, Horgan S, Savu MK, Cullen J, Chock A, Ramamoorthy S, Easter DW, Talamini MA. Hybrid natural orifice translumenal surgery (NOTES) sleeve gastrectomy: a feasibility study using an animal model. Surg Endosc. 2008;22(8):1798-802.

[116] Fischer LJ, Jacobsen G, Wong B, Thompson K, Bosia J, Talamini M, Horgan S. NOTES laparoscopic-assisted transvaginal sleeve gastrectomy in humans--description of preliminary experience in the United States. Surg Obes Relat Dis. 2009;5(5):633-6.

[117] Hagen ME1, Wagner OJ, Swain P, Pugin F, Buchs N, Caddedu M, Jamidar P, Fasel J, Morel P. Hybrid natural orifice transluminal endoscopic surgery (NOTES) for Roux-en-Y gastric bypass: an experimental surgical study in human cadavers. Endoscopy. 2008;40(11):918-24.

[118] Nau P, Anderson J, Yuh B, Muscarella P Jr, Christopher Ellison E, Happel L, Narula VK, Melvin WS, Hazey JW. Diagnostic transgastric endoscopic peritoneoscopy: extension of the initial human trial for staging of pancreatic head masses. Surg Endosc. 2010 ;24:1440-6.

[119] Michalik M, Orlowski M, Bobowicz M, Frask A, Trybull A. The first report on hybrid NOTES adjustable gastric banding in human. Obes Surg. 2011;21:524-7.

[120] Demura Y, Ishikawa N, Hirano Y, Inaki N, Matsunoki A, Watanabe G. Transrectal robotic natural orifice translumenal endoscopic surgery (NOTES) applied to intestinal anastomosis in a porcine intestine model. Surg Endosc. 2013; 27(12): 4693-701.

[121] Barthet M, Binmoeller KF, Vanbiervliet G, Gonzalez JM, Baron TH, Berdah S. Natural orifice transluminal endoscopic surgery gastroenterostomy with a biflanged lumen-apposing stent: first clinical experience (with videos). Gastrointest Endosc. 2015 ; 81(1):215-8.

[122] Tian Y, Wu SD, Chen YH, Wang DB. Transvaginal laparoscopic appendectomy simultaneously with vaginal hysterectomy: initial experience of 10 cases. Med Sci Monit. 2014;10(20):1897-901.

[123] Lehmann KS1, Zornig C, Arlt G, Butters M, Bulian DR, Manger R, Burghardt J, Runkel N, Pürschel A, Köninger J, Buhr HJ. [Natural orifice transluminal endoscopic surgery in Germany: Data from the German NOTES registry.] Chirurg. 2014 Jul 5 [Epub ahead of print].

[124] Yagci MA1, Kayaalp C1, Ates M1. Transvaginal appendectomy in morbidly obese patient. Case Rep Surg. 2014;2014:368640. doi: 10.1155/2014/368640.

[125] Knuth J, Heiss MM, Bulian DR. Transvaginal hybrid-NOTES appendectomy in routine clinical use: prospective analysis of 13 cases and description of the procedure. Surg Endosc. 2014;28(9):2661-5.

[126] Bernhardt J, Köhler P, Rieber F, Diederich M, Schneider-Koriath S, Steffen H, Ludwig K, Lamadé W. Pure NOTES sigmoid resection in an animal survival model. Endoscopy. 2012;44(3):265-9.

[127] Emhoff IA1, Lee GC, Sylla P. Transanal colorectal resection using natural orifice translumenal endoscopic surgery (NOTES). Dig Endosc. 2014 Jan;26(1):29-42.

[128] Chouillard E, Chahine E, Khoury G, Vinson-Bonnet B, Gumbs A, Azoulay D, Abdalla E. Notes total mesorectal excision (TME) for patients with rectal neoplasia: a preliminary experience.Surg Endosc 2014;28; (11):3150-7.

[129] Park SJ, Lee KY, Choi SI, Kang BM, Huh C, Choi DH, Lee CK. Pure NOTES rectosigmoid resection: transgastric endoscopic IMA dissection and transanal rectal mobilization in animal models. J Laparoendosc Adv Surg Tech A. 2013;23(7):592-5.

[130] Telem DA, Han KS, Kim MC, Ajari I, Sohn DK, Woods K, Kapur V, Sbeih MA, Perretta S, Rattner DW, Sylla P. Transanal rectosigmoid resection via natural orifice translumenal endoscopic surgery (NOTES) with total mesorectal excision in a large human cadaver series. Surg Endosc. 2013;27(1):74-80.

[131] Rieder E1, Spaun GO, Khajanchee YS, Martinec DV, Arnold BN, Smith Sehdev AE, Swanstrom LL, Whiteford MH. A natural orifice transrectal approach for oncologic resection of the rectosigmoid: an experimental study and comparison with conventional laparoscopy. Surg Endosc. 2011;25(10):3357-63.

[132] Lacy AM, Saavedra-Perez D, Bravo R, Adelsdorfer C, Aceituno M, Balust J. Minilaparoscopy-assisted natural orifice total colectomy: technical report of a minilaparoscopy-assisted transrectal resection. Surg Endosc. 2012;26(7):2080-5.

[133] Alba Mesa F, Amaya Cortijo A, Romero Fernandez JM, Komorowski AL, Sanchez Hurtado MA, Sanchez Margallo FM. Totally transvaginal resection of the descending colon in an experimental model. Surg Endosc. 2012;26(3):877-81.

[134] Li N, Zhang W, Yu D, Sun X, Wei M, Weng Y, Feng J. NOTES for surgical treatment of long-segment hirschsprung's disease: report of three cases. J Laparoendosc Adv Surg Tech A. 2013;23(12):1020-3.

[135] Spaun GO, Dunst CM, Arnold BN, Martinec DV, Cassera MA, Swanström LL.Transcervical heller myotomy using flexible endoscopy. J Gastrointest Surg. 2010;14:1902-9.

[136] Swanstrom LL, Dunst CM, Spaun GO. Future applications of flexible endoscopy in esophageal surgery. Gastrointest Surg. 2010;14 Supple 1:S127-32.

[137] Swanstorm LL, Rieder E, Duns CM. A stepwise approach and early clinical experience in peroral endoscopic myotomy for the treatment of achalasia and esophageal motility disorders. J Am Coll Surg. 2011;213:751-6.

[138] Rieder E, Martine DV, Duns CM, Sandstorm LL. Flexible endoscopic Zenkers diverticulotomy with a novel bipolar forceps: a pilot study and comparison with needleknife dissection. Surg Endosc. 2011;25:3273-8.

[139] Ishimaru T, Iwanaka T, Kawashima H, Terawaki K, Kodaka T, Suzuki K, Takahashi M. A pilot study of laparoscopic gastric pull-up by using the natural orifice translumenal endoscopic surgery technique: a novel procedure for treating long-gap esophageal atresia (type a). J Laparoendosc Adv Surg Tech A. 2011;21:851-7.

[140] Turner BG, Kim MC, Gee DW, Dursun A, Mino-Kenudson M, Huang ES, Sylla P, Rattner DW, Brugge WR. A prospective, randomized trial of esophageal submucosal tunnel closure with a stent versus no closure to secure a transesophageal natural orifice transluminal endoscopic surgery access site. Gastrointest Endosc. 2011;73:785-90.

[141] Turner BG, Cosigner S, Kim MC, Mino-Kenudson M, Ducharme RW, Surti VC. Stent placement provides safe esophageal closure in thoracic NOTES (TM) procedures. Surg Endosc. 2011; 25:913-8.

[142] Rolanda C, Silva D, Bronco C, Madeira I, Macedo G, Correia-Pinto J. Peroral esophageal segmentectomy and anastomosis with single transthoracic trocar: a step forward in thoracic NOTES. Endoscopy. 2011;43:14-20.

[143] Cho WY, Kim YJ, Cho JY, Bok GH, Jin SY, Lee TH, Kim HG, Kim JO, Lee JS. Hybrid natural orifice transluminal endoscopic surgery: endoscopic full-thickness resection of early gastric cancer and laparoscopic regional lymph node dissection - 14 human cases. Endoscopy. 2011;43:134-9.

[144] Abe N, Takeuchi H, Yanagida O, Masaki T, Mori T, Sugiyama M, Atomi Y. Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. Surg Endosc. 2009;23:1908-13.

[145] Chiu PW, Wai Ng EK, Teoh AY, Lam CC, Lau JY, Sung JJ. Transgastric endoluminal gastrojejunostomy: technical development from bench to animal study (with video). Gastrointest Endosc. 2010;71:390-3.

[146] Campos JM, Evangelista LF, Neto MP, Pagnossin G, Fernandes A, Ferraz AA, Ferraz EM. Translumenal endoscopic drainage of abdominal abscess due to early migration of adjustable gastric band. Obes Surg. 2010;20:247-50.

[147] Cahill RA, Asakuma M, Perretta S, Dallemagne B, Marescaux J. Gastric lymphatic mapping for sentinel node biopsy by natural orifice transluminal endoscopic surgery (NOTES). Surg Endosc. 2009;23 :1110-6.

[148] Luo H, Pan Y, Min L, Zhao L, Li J, Leung J, Xue L, Yin Z, Liu X, Liu Z, Sun A, Li C, Wu K, Guo X, Fan D. Transgastric endoscopic gastroenterostomy using a partially covered occluder: a canine feasibility study. Endoscopy. 2012;44:493-8.

[149] Ikeda K, Sumiyama K, Tajiri H, Yasuda K, Kitano S. Evaluation of a new multitasking platform for endoscopic full-thickness resection. Gastrointest Endosc. 2011;73:117-22.

[150] Lacy AM, Delgado S, Rojas OA, Ibarzabal A, Fernandez-Esparrach G, Taura P. Hybrid vaginal MA-NOS sleeve gastrectomy: technical note on the procedure in a patient. Surg Endosc. 2009;23:1130-7.

[151] Branco F, Pini G, Osório L, Cavadas V, Versos R, Gomes M, Authoring R, Correia-Pinto J, Lima E. Transvesical peritoneoscopy with rigid scope: feasibility study in human male cadaver. Surg Endosc. 2011;25:2015-9.

[152] Truong T, Arnaoutakis D, Awad ZT. Laparoscopic hybrid NOTES liver resection for metastatic colorectal cancer. Surg Laparosc Endosc Percutan Tech. 2012;22:e5-7.

[153] Shi H, Jiang SJ, Li B, Fu DK, Xin P, Wang YG. Natural orifice transluminal endoscopic wedge hepatic resection with a water-jet hybrid knife in a non-survival porcine model. World J Gastroenterol. 2011;17:926-31.

Chapter 6

Gastric Cardia and Gastroesophageal Junction — An Ongoing Challenge for the Endoscopist and the Pathologist

Alfredo J. A. Barbosa and Rivelle D. Pereira

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60554

Abstract

The cardiac mucosa of the human stomach is composed mainly of branched PAS positive mucous glands that occupy the deep half of the mucosa thickness. This morphological pattern of the mucous glands present in endoscopic biopsies from the gastric fundus region or near the gastroesophageal junction (GEJ) serves as parameter for the histological diagnosis of gastric cardia. However, this morphological pattern is highly variable along the gastric part of the GEJ: in some areas these mucous glands are abundant and in others they are scarce, if not totally absent. Depending on the concept adopted for some, the cardiac mucosa would be a native structure attached to human GEJ, while for others it would have a metaplastic origin that would occur during the extra-uterine life. In cardiac mucosa the mixed glands (mucous/oxyntic glands) are almost always present in between mucous glands and in between oxyntic glands; such as the parietal cells which could also be detected in greater or lesser amounts. The aim of this work was to evaluate the presence of serotonin-immunoreactive cells (EC cells) in these different types of glands in both normal cardiac mucosa as well as in the Barrett´s esophagus. The main results concerning the endocrinology of gastric cardia allows to consider that the human cardia has exocrine and endocrine elements that together constitute its specific differential characteristic in relation to the gastric fundus and to the antropyloric regions of the stomach. On the other hand, the histologic and immunohistochemical analysis of endoscopic biopsies of 26 patients showed that 23 (88.5%) of them presented varying amounts of mucous glands associated with intestinal metaplasia in distal esophagus. Moreover, many of these patients presented a rich component of serotoninergic EC cells. The major population

of serotonin-immunoreactive cells was found both in intestinal metaplasia as well as in its associated mucous glands. Among these patients, 16 (70%) presented foci of high concentration of serotoninergic EC cell in the distal esophagus. Whatever the neuroendocrine actions of serotonin in the GEJ, these actions should be enhanced in many patients who present a large population of EC cells in gastric cardia as well as in the areas of intestinal metaplasia of those with Barrett´s esophagus.

Keywords: Gastroesophageal junction, Cardiac mucosa, Endoscopy, Histology, Carditis, Barrett´s esophagus, Endocrine cells, Neuroendocrine cells, APUD cells

1. Introduction

The gastric cardia is generally defined as the area of mucosa located distal to the anatomic gastroesophageal junction (GEJ) and proximal to the oxyntic mucosa of the gastric body. It is an area of the stomach that raises many controversies about its native glandular components. The gastric cardia mucosa is absent in the stomach of some mammals species, such as rat and guinea pig; in others, such as swine, it covers a large area of the stomach competing for space with the body's mucosa [1].In humans it is very limited in size. The gastric cardia mucosa cannot be evaluated by standard endoscopy, or even through direct visual examination of surgical specimens or when performing necropsies. However, it can often be detected by histological examination of tissues removed from the gastric mucosa close to the GEJ. In most individuals the edges of cardiac mucosa have an irregular shape and also it has a variable average length, usually <2.0 cm. Mucous glands morphologically similar to those of the antral mucosa are found in this region in varying amounts, usually predominating over other histological types of glands, namely, the mixed glands (mixed mucous/oxyntic glands) and the oxyntic glands. The latter are morphologically identical to the oxyntic glands in the body and can occupy large areas of cardiac mucosa, juxtaposed to the squamocolumnar junction.

The gastric cardia mucosa is histologically very similar to the mucosa of the antral region, i.e., the foveolas are long occupying about half of the mucosa thickness which are composed of branched mucous glands that occupy the deep half of the mucosa thickness. This morphological pattern of the mucous glands of tissues collected by the endoscopist from the gastric fundus region or near the GEJ serves as parameter for the histological diagnosis of gastric cardia. This histological criterion is used by a large number of pathologists. However, due to the highly variable distribution of mucous glands along the gastric part of the GEJ, in some areas they are abundant and in others they are scarce, if not totally absent. In short, in some areas the pure mucous glands may be missing altogether, and replaced by mixed gland and/or oxyntic glands. Typical oxyntic glands are easily recognized by histology lining the human gastric body and the gastric fundus. This type of mucosa can be easily recognized in histological sections due to the high density of compact glands, rich in acidophilus parietal cells, and basophil zymogen cells. In this case, the histology of endoscopic samples does not reveal the presence of typical mucous glands, which may cause erroneous endoscopic–histologic

http://dx.doi.org/10.5772/60554

correlation. Because of the gastric cardia irregularity, divergent hypothesis arises on its real constitution and on its real presence in all subjects [2-5].

The cardiac mucosa also has a component of endocrine cells with unknown functions. This gap in knowledge about the importance of the endocrine population of the gastric cardia may be due to its conceptual status not yet well defined. In addition, the occurrence of local pathological processes of the GEJ modifies its structure hindering its proper identification. Among these processes the reflux esophagitis, the H. pylori infection, and the occurrence of intestinal metaplasia [6-8] should be mentioned.

2. Aims

Numerous endocrine cells stained with antibodies anti-chromogranin was found in gastric cardia in patients with endoscopically normal GEJ. This bunch of endocrine cells was found to be formed by a single population of serotonin-producing EC cells [9]. In gastrointestinal mucosa the serotonin-producing cells are also called "enterochromafin cells" (abbreviated: EC cells). It was then proposed that the EC cells were the only representatives of the rich gastric endocrine component of the gastric cardia. In the present work we studied standard endoscopic biopsies from the GEJ region aimed to assess the presence of different types of glands which occur in the gastric cardia and its component of serotoninergic EC cells. We also evaluated in a series of patients with Barrett's esophagus the different types of glands seen in the distal tubular esophagus and its content of serotonin-producing EC cells.

3. Material and methods

3.1. Histology and EC cells in gastric cardia

Endoscopic biopsies of two groups of consecutive patients attended at the Instituto Alfa de Gastroenterologia (IAG), Hospital das Clinicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil were studied. Group 1: made up of 21 patients who underwent upper gastrointestinal endoscopy in whom no significant changes of the esophagus and stomach were found. From these patients at least 2 biopsies containing cardiac mucosa were obtained from the area of the GEJ, and also 2 biopsies were obtained from each, antral and body mucosa of the stomach. Group 2: made up of 26 patients with endoscopic diagnosis of Barrett's esophagus (> 3 cm) in which at least 2 biopsies were performed for the diagnosis confirmation.

Sections of tissue were stained with Hematoxylin and Eosin (HE), Giemsa and PAS / Alcian Blue for histology. Ancillary stains used for cardiac mucosa analysis were: (1) immunohistochemical staining for demonstration of serotonin-producing EC cells using a primary monoclonal antibodies against serotonin (Dako A / S, Denmark), and (2) Grimelius staining for demonstration argyrophil cells [10]. Because of the irregularity of the gastric cardia

tissue specimens, the EC cells and argyrophil cells were quantified in glandular tissues where they presented the highest concentration (hot spot). In order to quantify the hot spot cell number, the high-power microscopic field was used and, thus, the number of cells/hpf was obtained. According to this criterion, the cell number was classified as few (<10/hpf) or numerous (≥10/hpf).

The presence of parietal cells in cardiac mucosa was evaluated in slides stained with HE. With this routine staining method these cells are easily recognizable, particularly in areas where they were numerous. In cases where they were not evident in HE preparations, or apparently very scarce, ancillary immunohistochemical stainingwas carried out using primary monoclonal antibodies against secretory canaliculi antigen of parietal cell (Barbosa, A.J.A., personal information).

3.2. EC cells in Barrett´s esophagus

Twenty six patients (mean age 36 years, range 22–69 years) with Barrett´s esophagus in whom at least 2 biopsies were performed for diagnostic confirmation were studied. All of them presented salmon-colored columnar mucosa extending in tongue-shaped projections at least 3 cm above the GEJ. The cases associated with gastrointestinal cancer and high-grade dysplasia of the columnar epithelium were excluded. Histological sections were reviewed to confirm the diagnosis and assessment of tissue structures present, namely, squamocolumnar junction, typical mucous glands, intestinal metaplasia with goblet cells, and the presence of hot spots of serotonin-immunoreactive EC cells. The quantitative evaluation of EC cells followed the same criterion as for the gastric cardia, i.e., few cells (<10 hpf) or numerous cells (≥10/hpf).

4. Results

4.1. Gastric cardia

Most of the 21 patients (mean age 36 years; range 22–69 years; 14 female) underwent endoscopy looking for obscure causes of anemia, obscure GI bleeding, or as a preoperative control. H. pylori was negative in 11 (52.4%) patients, both in cardiac mucosa and in the gastric body and antrum. Among these 11 patients 3 had the diagnosis of atrophic body gastritis (ABG). The histology results of the 8 remaining H. pylori-negative patients showed gastric mucosa of the antrum and body histologically normal and mononuclear inflammatory infiltration in cardiac mucosa. This inflammatory infiltrate was mild in 3 patients (mild carditis) and moderate in 5 patients (moderate carditis). Parietal cells were absent in cardiac mucosa of 4 H. pylori negative patients, 3 of them with ABG. In one patient, a small number of glands with goblet cells was found, indicating the presence of intestinal metaplasia (Table 1).

H. pylori infection occurred in 10 (47.6%) patients, and in 5 of these patients this microorganism was demonstrated in cardiac mucosa. The results of histology showed the presence of gastritis with mild inflammatory activity (+) or moderate (++) in the gastric mucosa of the antrum and body, with greater intensity in the antral mucosa. All patients in this subgroup had carditis of

http://dx.doi.org/10.5772/60554

Patient number	*Antrum/Corpus (HE)*	*Cardia (HE)*	*Cardia (H. pylori)*	*Antrum/Corpus (H. pylori)*	*Cardia Mucous glands/ PC*
2	N	+	-	-	PAS+ / PC+
3	N	+	-	-	PAS+ / PC+
8	N	++	-	-	PAS+ / PC+
13	N	+	-	-	PAS+ / PC+
18	N	++	-	-	PAS+IM+/PC+
19	N	++	-	-	PAS+ / PC+
20	N	++	-	-	PAS+ / PC+
22	N	++	-	-	PAS+ / PC+

N= Normal histology; +/++ = mild/moderate degree of inflammatory cells in lamina propria; PAS+ = Mucous glands present; IM+ = Intestinal metaplasia present; PC+ = Parietal cell present.

Table 1. Histology of the gastric mucosa of the antrum, corpus, and cardia of the 8 *H. pylori* negative patients. The 3 *H. pylori* negative patients with ABG were not included in this table.

moderate intensity, regardless of the presence of H. pylori. Typical parietal cells were present in the cardiac mucosa samples in varying amounts. In two patients PAS / AB staining revealed the presence of intestinal metaplasia foci in cardiac mucosa (Table 2).

Patient number	*Antrum/Corpus (HE)*	*Cardia (HE)*	*Cardia (H. pylori)*	*Antrum/Corpus (H. pylori)*	*Cardia Mucous glands/ PC*
1	++ / +	++	+	+	PAS+ / PC+
4	++ / +	++	+	+	PAS+ / PC +
5	++ / +	+	+	+	PAS+ / PC +
6	++ / +	++	-	+	PAS+ / CP+
9	++ / ++	++	-	+	PAS+IM+/PC+
10	+ / ++	++	-	+	PAS+ / PC +
11	++ / ++	++	-	+	PAS+ / PC +
14	+ / ++	++	-	+	PAS+ / PC -
15	++ / +	++	+	+	PAS+ / PC +
21	++ / ++	++	+	+	PAS+IM+/ PC+

+/++ =Mild/Moderate degree of inflammatory cells; PAS+ = Mucous glands present; IM+ = Intestinal metaplasia present; PC+ = Parietal cell present; PC– = Parietal cell absent.

Table 2. Histology of the gastric mucosa of the antrum, corpus, and cardia of the 10 *H. pylori* positive patients.

4.2. H. pylori, gastritis, and carditis

Inflammatory infiltrate of mononuclear cells and neutrophils (PMNs) were present in the gastric antrum and gastric body in all H. pylori positive patients and in the 3 patients with atrophic body gastritis. Mild or moderate chronic carditis was seen in all patients, regardless of the presence of the bacterium H. pylori (Table 2, Figure 1).

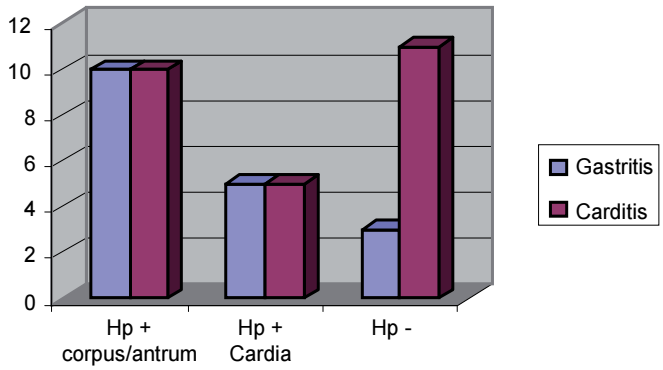

Figure 1. Presence of gastritis and carditis in *H. pylori* positive and *H. pylori* negative patients. The only three patients who were *H. pylori* negative with gastritis had ABG (type A gastritis).

4.3. Argyrophil and EC cells in gastric cardia

In 2 (9.5%) patients, argyrophil or serotonergic cells were not detected in the samples of cardiac mucosa. The number of patients with few argyrophil and EC cells (<10 / hpf) were similar, respectively, 38.1% vs 42.8%. Moreover, the number of patients presenting hot spots with numerous argyrophil and EC cells (≥10 / hpf) was also similar, respectively, 52.4% vs 47.6% (Figures 2 and 3).

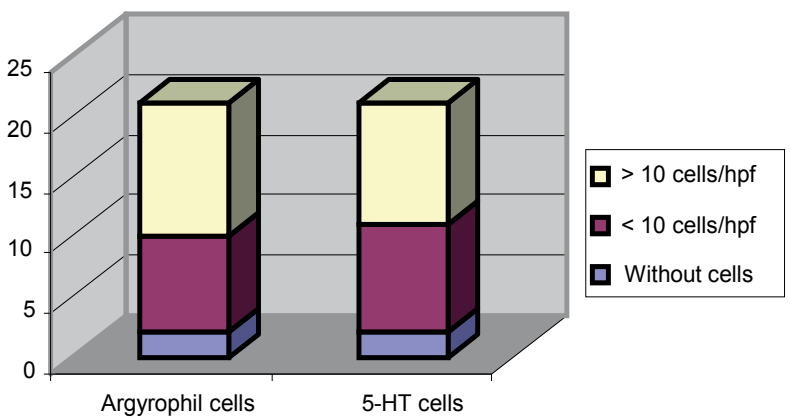

Figure 2. Quantitative relationship of argyrophil and 5HT- cells (EC cells) in cardiac mucosa of the 21 patients studied.

http://dx.doi.org/10.5772/60554

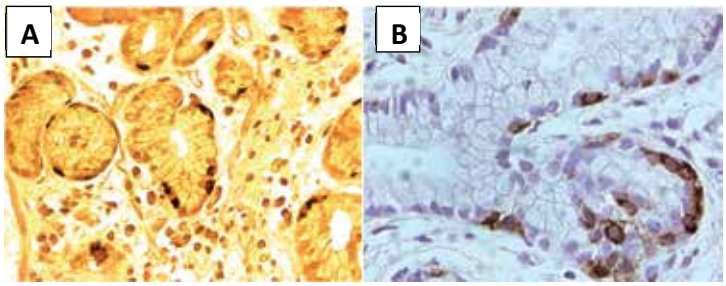

Figure 3. High-power photograph of the argyrophil (A) and serotoninergic (B) cells in mucous glands of the gastric cardia mucosa of patients with no endoscopic changes in the upper digestive tract.

4.4. Parietal cells in cardiac mucosa

The presence of parietal cells in histological sections of the cardiac mucosa was observed in 17 patients. Among them, 10 patients (47.6%) presented parietal cells relatively numerous and easily identifiable by routine staining; however, in 7 (33.3%) the parietal cells could only be identified with certainty by immunohistochemical staining. In 4 (19.1%) patients parietal cells were negative by routine staining and immunohistochemistry. Among them 3 had the diagnosis of atrophic body gastritis (Tables 1 and 2, Figure 4).

4.5. Barrett´s esophagus

In all 26 patients with Barrett's esophagus the presence of intestinal metaplasia with goblet cell was confirmed. In 23 (88.5%) of them, cardiac type mucous glands were present in tissue sections associated with intestinal metaplasia. In 2 of these patients no detectable EC cells were found in these glands. It should be considered that in most of the patients with Barrett´s esophagus the areas of intestinal metaplasia were significantly more extensive than the areas occupied by mucous glands. Oxyntic glands were not observed in Barrett's esophagus samples. The major EC cell concentrations were found both in areas of intestinal metaplasia and in areas occupied by mucous glands. In the 23 patients with mucous glands in the histological sections the foci of high concentrations of EC cells (≥ 10 / hpf) occurred in 16 (70%) of them. Similar frequency of high concentrations of serotonergic cells was observed in the areas of intestinal metaplasia: among the 26 patients studied 15 (58%) presented with numerous EC cells foci in metaplastic glands (Table 3, Figure 5).

Type of glands	n<10 EC cells/hpf	≥ 10 EC cells/hpf
Mucous (21/23)	05 (24%)	16 (76%)
IM (26/26)	11 (42%)	15 (58%)

IM = Intestinal metaplasia

Table 3. Type of glands present in the columnar mucosa of 26 patients with Barrett´s esophagus, and their concentration of few (< 10 EC cells/hpf) or numerous (≥ 10 EC cells/hpf) serotonin-immunoreactive cells.

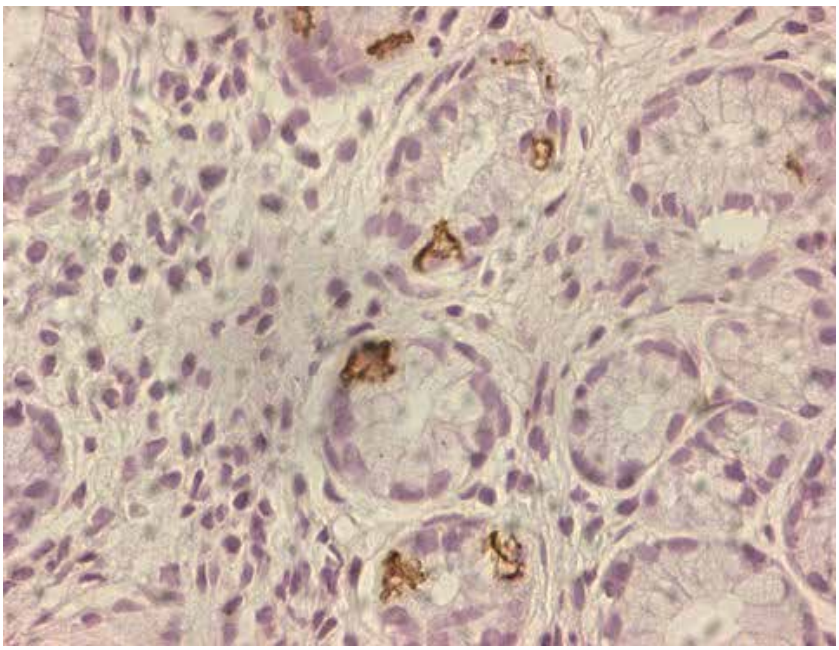

Figure 4. High-power photograph of gastric cardia mucosa composed mainly by mucous glands as a background of immunohistochemical staining. In between the mucinous cells there are few unexpected parietal cells with their secretory canaliculi stained in brown. A mild degree of mononuclear inflammatory cells is present in lamina propria.

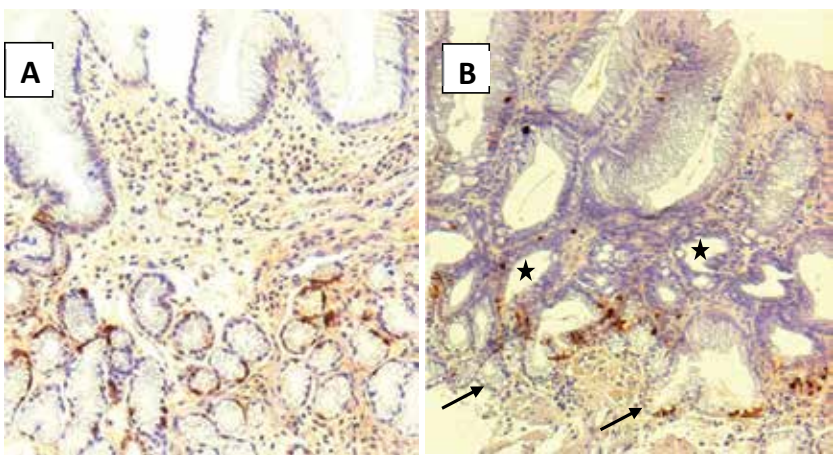

Figure 5. (A) Gastric cardia composed of mucinous columnar epithelium with underlying mucous glands that exhibit numerous serotonin-immunoreactive EC cells stained in brown. A mild degree of inflammatory mononuclear cells in lamina propria is present which seems to be a normal component of the gastric cardia in most individuals. (B) Barrett´s esophagus presenting the mucosa composed of mucinous columnar epithelium (upper side) with underlying glands presenting intestinal metaplasia (stars), and mucous glands in the bottom (arrows) of the photograph. Presence of serotonin-immunoreactive EC cells in both type of glands.

http://dx.doi.org/10.5772/60554

5. Discussion

Outside the limits of the standard endoscopy the mucosa of the gastric cardia remains an issue of much controversy due to its variable glandular constitution and its imprecise limits. Because there is no established knowledge about its functions this region of the stomach is usually relegated to the background when studying the physiology and pathophysiology of gastric mucosa. Usually cardiac mucosa is histologically defined as consisting of mucous glands which occupy the most proximal area of the gastric mucosa. It has a variable length, occupying an irregular band of approximately 0.5–2 cm in most individuals.

Many of the controversies in the literature about the status of the gastric cardia derive from concepts still poorly defined of its nature. Those who consider it to be a specific type of gastric mucosa characterized by the presence of well-defined lobes of PAS-positive mucous glands believe that the cardiac mucosa would occur only in a certain number of individuals, increasing its presence and extent progressively with age. Depending on the concept adopted, for some the cardiac mucosa would be a native structure attached to human GEJ, while for others it would have metaplastic origin that occurs during the extra-uterine life [2, 3].

Another question not always easy to answer is the definition of the GEJ. Often the endoscopist sets the GEJ as the transition area between squamous mucosa ends and the level of the rise of visible gastric folds. That is, in most individuals the GEJ can be endoscopically defined as the most proximal area of the stomach folds which represents the transition point between the squamous epithelium of the esophagus and the columnar mucus-secreting epithelium of the stomach, called Z line. However, this endoscopic criterion may be flawed due to frequent pathological changes that occur in this area. In these cases the Z line may move proximally and consequently taking anatomical position above GEJ [11].

We do not intend to discuss here the anatomical limits of the cardiac mucosa. At this point it would be better to forget the anatomical limits of the cardia and to turn our gaze to its morphological components. On the other hand, we should seek to learn about its seemingly exclusive endocrine component, made up of EC cells, a fact that is not usually taken into account in the conceptual controversies on this specific type of gastric mucosa. In general cardiac mucosa is understood as located in the most proximal region of the gastric mucosa, and presenting PAS-positive mucous glands and mixed glands whether or not accompanied by oxyntic glands. However, this concept only becomes complete after setting its endocrine pattern, characterized by a striking or exclusive presence of the population of EC cells. Once conceptualized thereby the cardiac mucosa would acquire its own characteristics making it distinct from the antropyloric and corpus mucosa of the stomach. Moreover, the gastric cardia also could acquire a greater degree of independence from endoscopic reports, since it would become possible to fit both its location in the stomach as in a heterotopic location of the distal esophagus, with or without the Barrett´s epithelium.

5.1. H. pylori and gastric cardia

It is well known that the standard endoscopy of the gastric mucosa does not relate well with the histological findings of H. pylori-associated gastritis of the antrum and corpus. The same

seems to happen with the cardiac mucosa in the absence of ulcerative lesions. In this series of 21 patients with endoscopically normal gastroesophageal mucosa, 10 (47.6%) had H. pylori infection and chronic gastritis of the antrum and corpus, and in 5 of these patients (50%) the bacteria were also identified in cardiac mucosa. However, all 10 patients had chronic carditis (Table 2). Chronic carditis with similar intensity was also observed in the 8 patients (38.1%) who were H. pylori-negative (Table 1).

The presence of H. pylori only in cardiac mucosa is not common. In nearly all cases if it is found in gastric cardia it should also be found in the gastric body or in antral regions. Therefore, all cases of H. pylori-positive chronic carditis will occur always with H. pylori-associated chronic gastritis [12]. On the other hand, regardless the presence of the bacteria, the carditis we found here had similar intensity in all 10 patients, H. pylori negative or positive. It is known that the main cause of inflammatory reaction of the gastric antrum and corpus is the H. pylori infection. In turn, the nonspecific inflammatory processes occurring in cardiac mucosa are frequently said to be a consequence of gastroesophageal reflux disease occurring in subclinical conditions, as appears to be the case of the present series of patients.

5.2. Parietal cells and gastric cardia

Atrophic body gastritis (ABG) occurred in 3 (14.3%) patients of the present series. The corpus glandular atrophy was due to the total depletion of oxyntic glands in the tissue samples that were examined. It should be noted that while this atrophy has been intense and easily identified by histology, it was unnoticed by standard endoscopy. This discrepant result, apparently surprising, is not at all uncommon in reports from hospital units of standard gastrointestinal endoscopy. ABG can also go undetected by routine histopathological examination, as a consequence of the morphological disruption getting the atrophic body's mucosa [13]. Most of the cases of ABG would have an autoimmune background, and thus it could explain the absence of parietal cells in the gastric cardia of the 3 patients with ABG, even using immunohistochemistry for the identification of these cells.

With the exception of the 3 patients with ABG only one patient among the other 18 subjects had no parietal cells in gastric cardia, which could be a sampling bias. This result shows that oxyntic glands with typical parietal cells easily demonstrated by HE staining are commonly found interposed between mucous and mixed glands. We think that this morphologic pattern is a common finding near to GEJ and could be considered as a normal structure of the human cardiac mucosa. In some cases, as seen in the present study, the parietal cells were apparently absent at the HE examination; nevertheless they could be identified by immunohistochemical staining (Figure 4). In areas of the GEJ where parietal cells are abundant, frequently juxtaposed to the squamocolumnar junction, the examiner may have the false impression about possible absence of cardiac mucosa [14].

In cardiac mucosa the mixed glands are almost always present in between mucous glands and in between oxyntic glands; such as the parietal cells which could also be detected in greater or lesser amounts [7]. Thus, the concept of human cardiac mucosa should cover this large range of different types of glands and in different proportions.

http://dx.doi.org/10.5772/60554

5.3. Endocrine component of the gastric cardia

The population of endocrine cells of the human cardiac mucosa is almost entirely, if not all, constituted by serotonin producing EC cells. EC cells have high affinity for silver salts, which is frequently employed to stain these cells. Two general silver methods may be used for this purpose, the argentaffin (Fontana-Masson method) and the argyrophilic stains. Among the latter the Grimelius method seems to be the most widely used.

At this point we should remember that: (a) the EC cells are argentaffin cells and can be easily stained in ammoniacal silver nitrate solution and this method can be applied to reveal gastrointestinal EC cells from different animal species [15]; (b) EC cells, as being argentaffin, can also be stained by the Grimelius indirect argyrophilic method; (c) the EC cells could not only produce serotonin; there are subsets of these cells that express, in addition to serotonin, different peptidergic hormones [16-18]; (d) finally it should be remembered that there are numerous different types of neuroendocrine cells which produce different peptides and having the same argyrophilic properties described above. In fact, almost all the neuroendocrine cells of the digestive tract of man can be easily demonstrated by Grimelius staining method. In the present study, we found that the population of serotonin-producing EC cells in gastric cardia, specifically demonstrated by immunohistochemistry, was roughly equivalent to the population of argyrophil cells.

Our results concerning the endocrinology of gastric cardia, along with those previously published by others, allow to consider that the human cardia, although occupying a restricted area of the stomach, has exocrine and endocrine elements that together constitute its differential characteristic (maybe specific) in relation to the gastric fundus and the antropyloric regions. Briefly, it could be said that in the antral mucosa the EC cells divide the space mainly with the G cells (gastrin) and D cells (somatostatin). In turn, in the body region of the human stomach EC cells are rare or absent, giving space mainly for the enterochromaffin-like (ECL) cells, the most numerous in this region. Finally, in the gastric cardia the EC cells are numerous and constitute the sole or predominant cell type (Figure 6).

Therefore, considering all the exocrine and endocrine elements of the human gastric cardia, many controversies reported in the literature on its morphological characteristics and also about its definition seem to be half-finished. Usually these discussions are mainly based on arguments related to its histologically most characteristic exocrine component, i.e., the presence of PAS-positive mucous glands [3]. At this point it could be summarized regarding the anatomy of the human gastric cardia mucosa: [i] a wide variation of different types of exocrine glands and [ii] the presence of a large number of serotoninergic EC cells in mucous glands and in mucous/oxyntic glands (mixed glands).

Serotonin (5-HT) seems to present important neuroendocrine functions in different segments of the gastrointestinal tract, including the control of gastrointestinal motility. Serotonin functions are mediated via specific receptors [19-21]. Some of these receptors have been described recently in the lower esophageal sphincter (LES) and the authors speculate on the role of serotonin in the modulation of its activity [22]. The 5HT1 and 5HT7 receptors are considered to be muscle relaxation promoters while 5HT2, 5HT3, and 5HT4 to be stimulating

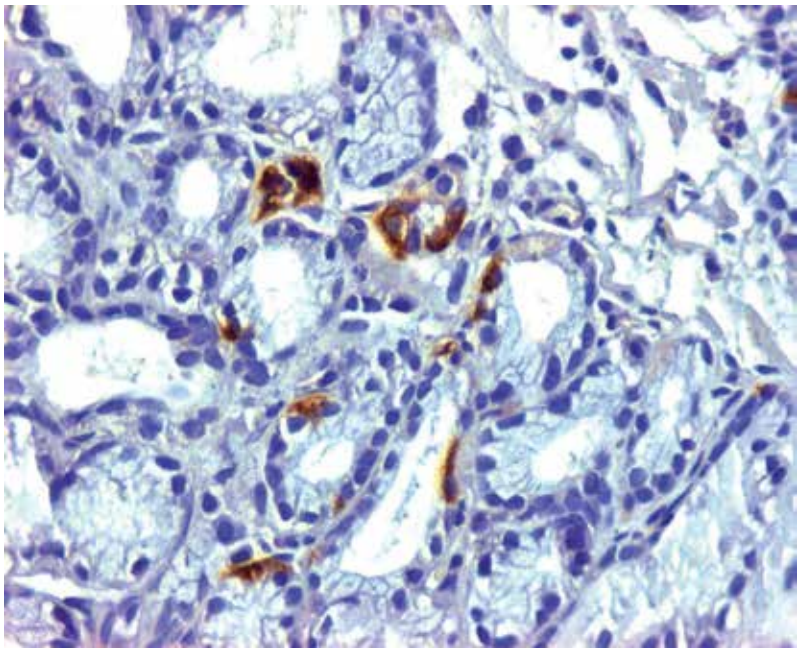

Figure 6. High-power microscopic field shows a marked number (> 10 cells/hpf) of serotonin-immunoreactive EC cells in mucous glands of the gastric cardia. The EC cells appear to be the only (or largely predominanting) population of endocrine cells in this region of the human stomach. This fact seems to be characteristic of these mucous glands, and as such it should be included in the morphological definition of the human gastric cardia.

muscle contraction [23-25]. Therefore, the frequent and relatively abundant presence of serotonergic cells in the human gastric cardia, next to GEJ, could act as a modulating factor of the neuromuscular activity of the LES. The disruption of LES functional activity is considered nowadays as the main cause of the gastroesophageal reflux disease, frequent pathological condition in the general population, and the main cause of reflux esophagitis and Barrett's esophagus.

5.4. Serotoninergic cells and Barrett´s esophagus

The diagnosis of Barrett's esophagus requires endoscopic evidence showing columnar mucosa above the GEJ, lining the distal esophagus, and this change must be confirmed by histopathological analysis. Thus, the result of histology should confirm the presence of columnar epithelium emphasizing the presence of goblet cells. Endoscopicaly the GEJ is identified as being the most proximal area to the start of gastric folds. Therefore, projections shaped like red salmon–color tongues above this area, lining the distal esophagus, are interpreted by the endoscopist as Barrett's esophagus. Macroscopically, these red-salmon tongues are often quite irregular in their proximal limits, and the microscopic foci of intestinal metaplasia, with or without goblet cells, can also have an irregular distribution.

Therefore, when biopsies are done near the limits of salmon-red areas the histopathological results can reveal the squamocolumnar junction in the absence of intestinal metaplasia. That

http://dx.doi.org/10.5772/60554

is, the histological examination may notice the presence of columnar mucosa composed mainly by glands lined by mucous-secreting epithelium with or without brush border, and with mucous cardiac-like glands, however, without the presence of goblet cells. In general, the North American gastroenterology societies require the presence of goblet cells to confirm the intestinal metaplasia and, consequently, the diagnosis of Barrett's esophagus; differently, the British societies admit that the presence of columnar epithelium lining the esophagus with cardiac type mucous glands can be accepted as a criterion for the definitive diagnosis of Barrett's esophagus [26, 27].

Regardless of this conceptual controversy on the definition of Barrett´s esophagus it should be stressed the presence of the abundant serotoninergic cells in the intestinal-, and cardiac-type glands that cover the inner wall of the tubular esophagus. These groups of cardiac-type glands are found frequently in endoscopic biopsies of Barrett's esophagus and seem to have preserved their rich component of serotonergic cells. The analysis of the present series of biopsy fragments showed that among patients with Barrett's esophagus, 23 (88.5%) of them showed varying amounts of mucous glands associated with intestinal metaplasia; among these patients, 16 (70%) had foci with high concentration of serotoninergic EC cells.

Therefore, it seems to happen in Barrett's esophagus a fertile soil for serotonergic cells proliferation since they can replicate themselves both in the cardiac-like epithelium as in the intestinal metaplastic glands. Mucous glands present in the tubular esophagus and associated with intestinal metaplasia do not have a well-explained histogenesis. Whether metaplastic or not, they are mirror images of its sisters present in the normal gastric cardia, even as a depository of serotonergic cells. Whatever the neuroendocrine actions of serotonin in the lower esophagus, these actions should be enhanced in large number of patients with Barrett's esophagus, because of the simultaneous presence in these patients of the extra population of serotoninergic cells present in the areas of intestinal metaplasia.

We have seen that in the normal gastric cardia the population of argyrophil cells is represented almost entirely by the serotoninergic EC cells. However, in the areas of Barrett's intestinal metaplasia the population of argyrophil cells should be a more diverse bunch of endocrine cells since the intestinal mucosa is a rich depository of different types of these cells. Indeed, immunohistochemical studies of Barrett's esophagus demonstrated not only the significant presence of EC cells as well as varying numbers of immunoreactive cells to somatostatin, motilin, pancreatic peptide, gastrin, glucagon, secretin, and neurotensin. These findings led the authors to propose that Barrett's epithelium would be derived from multipotent stem cells with ability to differentiate into gastric and intestinal epithelium [28, 29].

Although 30 years have passed after the first suspicions by Buchan, Rindi, and colleagues about the multipotent stem cells as an explanation for the histogenesis of Barrett's epithelium, it still remains in the territory of speculations. Nowadays various hypothesis of multipotential stem cells are still in focus. It is proposed that these stem cells would be derived from the bone marrow, or from the basal layer of the squamous epithelium or from the mucous gland ducts located in the submucosa of the esophagus. Other possibility would be the possible remaining of embryonic tissues in the area of GEJ. Similar issues occur nowadays regarding the histo-

genesis of the epithelium of the human gastric cardia. From what we see, here too we have no definitive answers.

Acknowledgements

This work was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Distrito Federal, Brasil, and by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Belo Horizonte, Brasil.The authors thank Ms. Luciene S. P. Faria, from the IAG Laboratory of Gastrointestinal Histopathology, for technical assistance.

Author details

Alfredo J. A. Barbosa[1,2*] and Rivelle D. Pereira[1]

*Address all correspondence to: abarbosa@medicina.ufmg.br

1 Laboratory of Digestive and Neuroendocrine Pathology, UFMG, Belo Horizonte, Brazil

2 Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), and Instituto Alfa de Gastroenterologia do Hospital das Clínicas, UFMG, Belo Horizonte, Brazil

References

[1] Barbosa AJA, Silva JC, Nogueira AMMF, Paulino Junior E, Miranda CR. Higher incidence of Gastrospirillum sp. in swine with gastric ulcer of the pars oesophagea. Veterinary pathology. 1995 Mar;32(2):134-9. PubMed PMID: 7771053.

[2] Chandrasoma PT, Der R, Ma Y, Dalton P, Taira M. Histology of the gastroesophageal junction: an autopsy study. The American journal of surgical pathology. 2000 Mar; 24(3):402-9. PubMed PMID: 10716154.

[3] Kilgore SP, Ormsby AH, Gramlich TL, Rice TW, Richter JE, Falk GW, et al. The gastric cardia: fact or fiction? The American journal of gastroenterology. 2000 Apr;95(4): 921-4. PubMed PMID: 10763938.

[4] Zhou H, Greco MA, Daum F, Kahn E. Origin of cardiac mucosa: ontogenic consideration. Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society. 2001 Jul-Aug;4(4):358-63. PubMed PMID: 11441337.

[5] Glickman JN, Chen YY, Wang HH, Antonioli DA, Odze RD. Phenotypic characteristics of a distinctive multilayered epithelium suggests that it is a precursor in the development of Barrett's esophagus. The American journal of surgical pathology. 2001 May;25(5):569-78. PubMed PMID: 11342767.

[6] Malfertheiner P, Peitz U. The interplay between Helicobacter pylori, gastro-oesophageal reflux disease, and intestinal metaplasia. Gut. 2005 Mar;54 Suppl 1:i13-20. PubMed PMID: 15711003. Pubmed Central PMCID: 1867793.

[7] Odze RD. Pathology of the gastroesophageal junction. Seminars in diagnostic pathology. 2005 Nov;22(4):256-65. PubMed PMID: 16939053.

[8] Ringhofer C, Lenglinger J, Izay B, Kolarik K, Zacherl J, Eisler M, et al. Histopathology of the endoscopic esophagogastric junction in patients with gastroesophageal reflux disease. Wiener klinische Wochenschrift. 2008;120(11-12):350-9. PubMed PMID: 18709523.

[9] Voutilainen M, Juhola M, Pitkanen R, Farkkila M, Sipponen P. Immunohistochemical study of neuroendocrine cells at the gastric cardia mucosa. Journal of clinical pathology. 2002 Oct;55(10):767-9. PubMed PMID: WOS:000178513100011. English.

[10] Grimelius L, Wilander E. Silver stains in the study of endocrine cells of the gut and pancreas. Investigative & cell pathology. 1980 Jan-Mar;3(1):3-12. PubMed PMID: 6156147.

[11] Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus--the need for standardization of the definition and of endoscopic criteria. The American journal of gastroenterology. 1998 Jul;93(7):1033-6. PubMed PMID: 9672325.

[12] Genta RM, Huberman RM, Graham DY. The gastric cardia in Helicobacter pylori infection. Human pathology. 1994 Sep;25(9):915-9. PubMed PMID: 8088767.

[13] Barbosa AJA, Miranda CG Atrophic body gastritis: A challenge for the presumptive endoscopic and histologic diagnosis of autoimmune gastritis. In: Pascu O, editor. Gastrointestinal endoscopy. Rijeka, Croatia: InTech; 2011. p. 169-82.

[14] Sarbia M, Donner A, Gabbert HE. Histopathology of the gastroesophageal junction: a study on 36 operation specimens. The American journal of surgical pathology. 2002 Sep;26(9):1207-12. PubMed PMID: 12218577.

[15] Barbosa AJA, Castro LPF,, Nogueira AMMF. A simple and economical modification of the Masson-Fontana method for staining melanin granules and enterochromaffin cells. Stain technology. 1984 Jul;59(4):193-6. PubMed PMID: 6208641.

[16] Pearse AG, Polak JM. Immunocytochemical localization of substance P in mammalian intestine. Histochemistry. 1975;41(4):373-5. PubMed PMID: 1095530.

[17] Alumets J, Hakanson R, Sundler F, Chang KJ. Leu-enkephalin-like material in nerves and enterochromaffin cells in the gut. An immunohistochemical study. Histochemistry. 1978 Jul 12;56(3-4):187-96. PubMed PMID: 99394.

[18] Heitz PU, Kasper M, Krey G, Polak JM, Pearse AG. Immunoelectron cytochemical localization of motilin in human duodenal enterochromaffin cells. Gastroenterology. 1978 Apr;74(4):713-7. PubMed PMID: 344128.

[19] Hempfling C, Neuhuber WL, Worl J. Serotonin-immunoreactive neurons and mast cells in the mouse esophagus suggest involvement of serotonin in both motility control and neuroimmune interactions. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2012 Jan;24(1):e67-78. PubMed PMID: 22029710.

[20] Li Z, Chalazonitis A, Huang YY, Mann JJ, Margolis KG, Yang QM, et al. Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. The Journal of neuroscience : the official journal of the society for neuroscience. 2011 Jun 15;31(24):8998-9009. PubMed PMID: 21677183.

[21] Kapeller J, Moller D, Lasitschka F, Autschbach F, Hovius R, Rappold G, et al. Serotonin receptor diversity in the human colon: Expression of serotonin type 3 receptor subunits 5-HT3C, 5-HT3D, and 5-HT3E. The journal of comparative neurology. 2011 Feb 15;519(3):420-32. PubMed PMID: 21192076. Pubmed Central PMCID: 3056486.

[22] Li HF, Liu JF, Zhang K, Feng Y. Expression of serotonin receptors in human lower esophageal sphincter. Experimental and therapeutic medicine. 2015 Jan;9(1):49-54. PubMed PMID: 25452775. Pubmed Central PMCID: 4247306.

[23] Prins NH, Van Der Grijn A, Lefebvre RA, Akkermans LM, Schuurkes JA. 5-HT(4) receptors mediating enhancement of contractility in canine stomach; an in vitro and in vivo study. British journal of pharmacology. 2001 Apr;132(8):1941-7. PubMed PMID: 11309267. Pubmed Central PMCID: 1572724.

[24] Janssen P, Prins NH, Meulemans AL, Lefebvre RA. Pharmacological characterization of the 5-HT receptors mediating contraction and relaxation of canine isolated proximal stomach smooth muscle. British journal of pharmacology. 2002 May;136(2):321-9. PubMed PMID: 12010782. Pubmed Central PMCID: 1573351.

[25] Janssen P, Prins NH, Moreaux B, Meulemans AL, Lefebvre RA. In vivo characterization of 5-HT1A receptor-mediated gastric relaxation in conscious dogs. British journal of pharmacology. 2003 Nov;140(5):913-20. PubMed PMID: 14517177. Pubmed Central PMCID: 1574099.

[26] Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ, American Gastroenterological A. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):e18-52; quiz e13. PubMed PMID: 21376939. Pubmed Central PMCID: 3258495.

[27] Fitzgerald RC, Di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014 Jan;63(1):7-42. PubMed PMID: 24165758.

[28] Rindi G, Bishop AE, Daly MJ, Isaacs P, Lee FI, Polak JM. A mixed pattern of endocrine cells in metaplastic Barrett's oesophagus. Evidence that the epithelium derives from a pluripotential stem cell. Histochemistry. 1987;87(4):377-83. PubMed PMID: 2447038.

[29] Buchan AM, Grant S, Freeman HJ. Regulatory peptides in Barrett's oesophagus. The journal of pathology. 1985 Jul;146(3):227-34. PubMed PMID: 2863340.

Chapter 7

The Diagnosis and Treatment of Early-Stage Colorectal Cancer

Taku Sakamoto, Masayoshi Yamada,
Takeshi Nakajima, Takahisa Matsuda and
Yutaka Saito

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60760

Abstract

The introduction of colorectal endoscopic submucosal dissection (ESD) has expanded the applications for endoscopic treatment; as a result, lesions with low metastatic potential can be treated endoscopically regardless of the lesion size. The most attractive feature of ESD is the achievement of en bloc resection with a lower local recurrence rate in comparison to that of endoscopic piecemeal mucosal resection. However, in case of gastric cancers, ESD is not as widely applied to the treatment of colorectal neoplasms because of its technical difficulty, longer procedural time, and increased perforation risk. In the movement toward diversified endoscopic treatment strategies for superficial colorectal neoplasms, endoscopists who begin to perform ESD need to recognize the indications of ESD, as well as the technical issues and associated complications of this procedure.

Keywords: Superficial colorectal neoplasm, pit pattern, endoscopic submucosal dissection

1. Introduction

Endoscopic therapy is a major step forward in the management of early-stage gastrointestinal cancers. In the colorectum, lymph node metastasis always occurs only with deep invasion of

the submucosa (≥1000 μm), and lesions that are diagnosed as well-differentiated adenocarcinomas that are limited to the mucosa (intramucosal) or that superficially invade the submucosa (<1,000 μm from the muscularis mucosa) without lymphovascular invasion or a component with poor differentiation component (or both) are usually considered to not involve lymph node metastasis [1-3]. Among these factors, however, only the depth of invasion can be estimated by endoscopy prior to treatment. Thus, the depth of invasion must be accurately estimated before any therapeutic decision is made. Endoscopic resection plays two important roles in gastrointestinal surgery: achieving curative resection and allowing an accurate histological evaluation of lesions. As lesions measuring more than (or equal to) 10 mm have the potential for malignancy, they should be resected en bloc to avoid either residual or recurrent lesions (or both) [4].

Endoscopic submucosal dissection (ESD) is a state-of-the art technique for the treatment of large colorectal neoplasms that enables en bloc resection regardless of lesion size [5-8]. This chapter describes in detail the method for estimating depth invasion and ESD for colorectal neoplasms.

2. Diagnosis

Magnifying observation techniques, including chromoendoscopy and narrow-band imaging (NBI), have been recognized as high-precision methods for the diagnosis of depth invasion. With NBI, avascular or loose vascular findings are considered a key indicator of a submucosal and deep invasive cancer [9, 10]. However, NBI is a relatively new method with an unknown learning curve and different classifications, even within a single country like Japan. In contrast, pit pattern analysis using crystal violet staining has now become standardized due to its longer availability and one-to-one comparisons of endoscopic and pathological findings. In our view, pit pattern analysis is the most reliable predictor of depth invasion. During this analysis, each lesion should be confirmed to include a non-invasive pattern and Type V pit(s) with clearly demarcated areas, as this indicates that the lesion is suitable for endoscopic mucosal resection (EMR) or ESD with an estimated depth of invasion less than that of a submucosal invasive cancer [11].

In this section of the chapter, we will describe in order of the actual clinical process an endoscopic evaluation focused on the invasion depth of an early colorectal cancer, which is defined as confirmed cancer cells present in the mucosa or the submucosa, regardless of lymph node metastasis.

2.1. White-light non-magnifying endoscopy

The first diagnostic step is determination of the macroscopic lesion type. Most early-stage colorectal cancer lesions are classified as Type 0 according to Borrmann classification, which is equivalent to a superficial lesion in the Paris classification. In the latter classification, superficial lesions are divided into two groups: polypoid and non-polypoid lesions; in particular, non-polypoid lesions have received considerable attention, given their clinical

http://dx.doi.org/10.5772/60760

importance. Non-polypoid lesions include superficial elevated (0-IIa), completely flat (0-IIb), and depressed (0-IIc) lesions. Moreover, a superficial-type lesion of size more than 10 mm with no increase in height is called a laterally spreading tumor (LST). LSTs can be further divided into two main classes: granular type (LST-G) and non-granular type (LST-NG) (Figure 1). We know that LST-NG tumors of size more than (or equal to) 20 mm and LST-G tumors of size more than (or equal to) 30 mm harbor a significantly higher likelihood of submucosal invasion [12]; therefore, a careful evaluation of morphological features is crucial for the depth diagnosis.

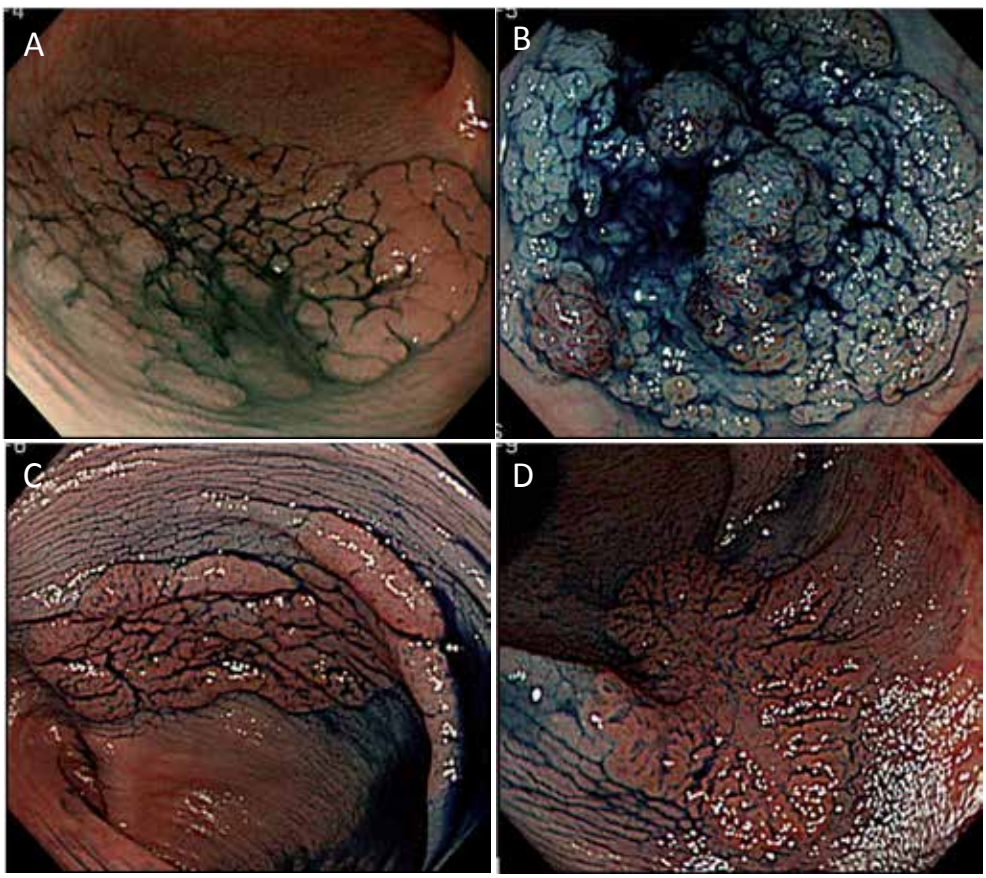

Figure 1. Subtypes of tumors with lateral spread. A: Laterally spreading tumor (LST), homogeneous granular type; B: LST, mixed granular type; C: LST, non-granular, flat elevated type; D: LST, non-granular, pseudodepressed type.

Some findings regarding the important conventional colonoscopic findings for determining the invasion depths of non-polypoid lesions have been reported in previous studies: redness, white spots (chicken-skin appearance), appearance of expansion, firm consistency, deep depression surface, irregular bottom of depression surface, and fold converging toward the tumor. Matsuda et al. verified these findings retrospectively to clarify the clinically important characteristics. White spots, redness, firm consistency, and a deep depressed area were

significantly associated with an increased risk of submucosal deep invasion in a univariate analysis [13].

2.2. Narrow-band imaging with magnifying endoscopy

NBI is an innovative optical technology that uses interference filters for spectral narrowing of the bandwidth used in conventional white-light medical videoscopy. NBI allows a more detailed visualization of the mucosal architecture and capillary pattern without the need for dye spraying. Upon reviewing microvascular architecture using NBI, our institution identified four different patterns according to Sano classification [9]. By examining a lesion's microvessel pattern using NBI, invasion depth was subsequently classified as intramucosa/shallow submucosa (lack of uniformity and high vessel density; capillary pattern IIIA) or deep submucosa (nearly avascular or loose microvessel diameters; capillary pattern IIIB). Ikematsu et al. reported the diagnostic accuracy of this technique for determining the invasion depth as follows: the sensitivity, specificity, and diagnostic accuracy of capillary pattern IIIB for differentiating the intramucosa/shallow submucosa from deep submucosa were 84.8%, 88.7%, and 87.7%, respectively [9].

On the other hand, we assessed the interobserver agreement in terms of estimating the depth of invasion using NBI and pit pattern analysis and found substantial agreement with pit pattern analysis and moderate agreement for NBI with magnification [14]. Regarding the lower interobserver agreement in the interpretation of the NBI findings, we should remember that the NBI system is still a relatively new diagnostic method with an unknown learning curve; to complicate the matter, several different classifications for the evaluation of mucosal morphology in colorectal neoplasms have been proposed recently in Japan. Regarding a consensus on the microvascular architecture and classification of findings, there has not been sufficient discussion for the worldwide use of NBI to become a reality.

2.3. Pit pattern evaluation using crystal violet staining

According to the classification of colonic crypts described by Kudo and Tsuruta, type V pit patterns include areas of irregular crypts (type V_I) and apparently non-structured areas (type V_N). Type V_I pit patterns allow further subdivision into areas with mild irregularity (type V_I mild) and severe irregularity that show destroyed and severely damaged pits (type V_I severe). Type V_I severe pit patterns were defined by Tobaru et al. as areas containing pits with poor demarcation and those which contain faded or unstained stromal areas [15]. Regarding diagnostic standardization by magnifying chromoendoscopy, this classification should be directly linked to the choice of the most appropriate treatment. The depth of invasion of an early colorectal cancer is normally determined from the accumulated data of serial observations, which includes conventional imaging with no magnification. In this regard, Matsuda et al. described the clinical classification of an "invasive/non-invasive pattern" that incorporates conventional observations of lesion configuration, including depression, large nodules, and reddened areas (Figure 2) [13]. When differentiating between intramucosal/shallow submucosal lesions and deep submucosal lesions, an interpretation using this invasive pattern demonstrated a sensitivity of 85.6% and a specificity of 99.4%. In this report, the diagnostic

http://dx.doi.org/10.5772/60760

accuracy was sufficient to demonstrate the efficacy of magnifying chromoendoscopy, and the clear advantage of this classification was directly reflected in the choice of treatment: endoscopic or surgical resection. Based on the pit pattern classification, the invasive pattern might include some cases classified as V_I severe and V_N pit patterns.

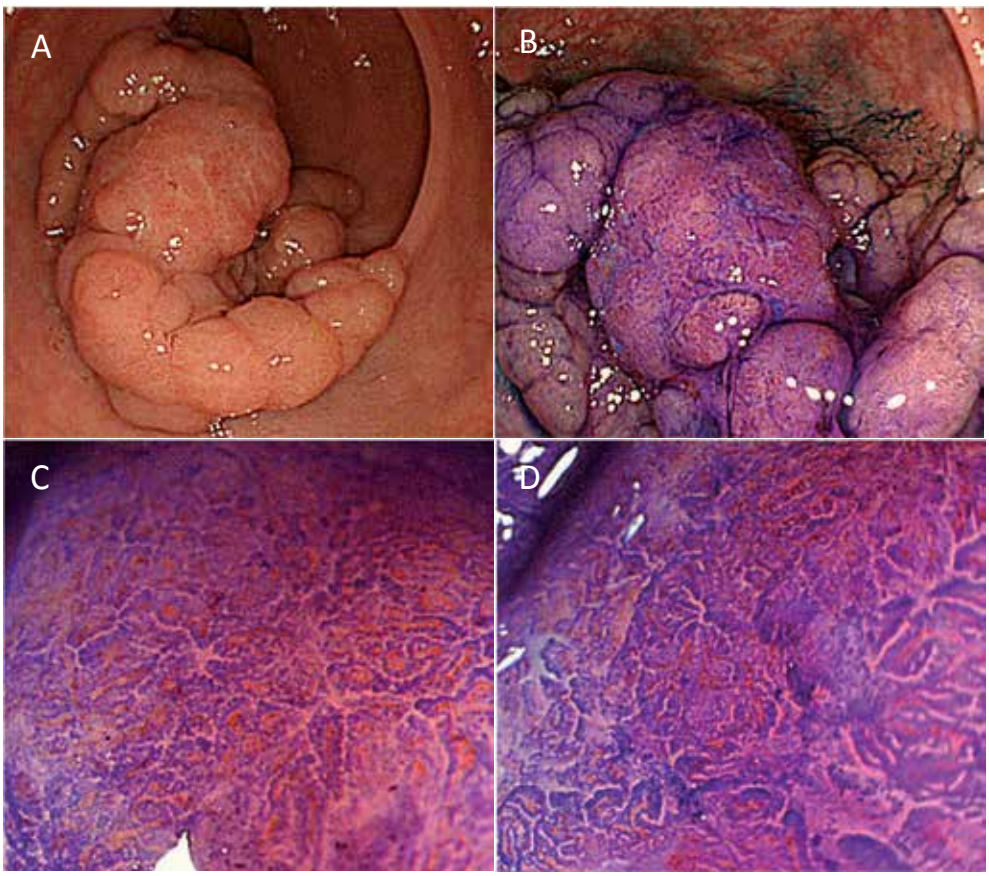

Figure 2. An invasive lesion exhibiting the "invasive pattern" visualized by magnifying chromoendoscopy with crystal violet staining. A: Large lesions with a reddish, protruding component; B: Depth diagnosis should focus on the reddish part; C, D: Reddish part displays a highly irregular type VI pit, which was demarcated as the reddish area.

2.4. Alternatives

2.4.1. Endoscopic ultrasonography

Data on the utility of high-frequency endoscopic ultrasonography (EUS) for the management of the malignant colorectal polyps is conflicting. Some previous reports have demonstrated the usefulness of EUS, in particular the advantages of high-frequency ultrasound for diagnosing the invasion depth of early colorectal cancer [16-19]. Hurlstone et al. reported that high-

frequency ultrasound was superior to magnifying chromoendoscopy for determining depth invasion (accuracy of 93% vs. 59%, respectively). Matsumoto et al. also demonstrated the diagnostic superiority of EUS (probe-EUS) in their study (negative predictive value for deep invasion of 91% vs. 54%, respectively) [19]. In contrast, Fu et al. reported that there was no significant difference between magnifying chromoendoscopy and EUS for the preoperative staging of early colorectal cancer [20].

EUS is definitely very useful for determining the invasion depth or predicting submucosal fibrosis in flat or depressed lesions; however, its limited penetration depth is a recognized disadvantage. In particular, it might be difficult to accurately evaluate the invasion depth or submucosal fibrosis in protruding lesions. Moreover, the use of EUS to observe lesions located on the oral side of folds is also considered difficult.

2.4.2. Non-lifting sign

Uno et al. first described the "non-lifting sign" in 1994 [21]. Lesion observation during and after submucosal saline injection is a simple and crucial method for not only assessing the potential for deep invasion but also predicting the technical difficulty of endoscopic resection. Lesions may not lift as a result of submucosal fibrosis, a desmoplastic reaction, or the presence of large amounts of elastic fibers in vessels [22].

Regarding the diagnostic accuracy of the non-lifting sign for predicting deep invasion, Kobayashi et al. reported a sensitivity of 62% and specificity of 98%. However, magnifying chromoendoscopy displayed a sensitivity of 85% and specificity of 98% in the same study, resulting in a significant difference in sensitivity [23]. Therefore, despite its simplicity, the non-lifting sign could not reliably predict deep invasion when compared with a magnifying observation.

3. Indication of endoscopic treatment

In Japan, colorectal ESD has been covered under health insurance since 2012. Before 2012, the performance of colorectal ESD was allowed at only a restricted number of advanced medical centers that had been approved in 2009 by the Japanese Ministry of Health, Labor, and Welfare. From this, "The Colon ESD Standardization Implementation Working Group," a sub-organization of the "Gastroenterological Endoscopy Promotion Liaison Conference," produced a draft titled "Criteria of Indications for Colorectal ESD" [24]. In essence, ESD is indicated when lesions require en bloc resection for evaluation of histological features and for lesions whose resection using conventional EMR techniques is problematic. In other words, cancerous lesions that have the potential to invade the submucosal layer require treatment using ESD. In these cases, the size and morphology of the lesion are considered as critical factors. For example, a nodular mixed type LST of size more than (or equal to) 30 mm and an LST-NG of size more than (or equal to) 20 mm are considered to contain some risk of an invasive component. In addition, lesions for which resection is technically difficult via conventional EMR are also considered an indication for ESD; these include lesions exhibiting the non-lifting sign after

http://dx.doi.org/10.5772/60760

submucosal injection, local recurrent lesions following previous treatment, and relatively large protruding-type lesions (except pedunculated polyps). In general, the en bloc resection of large neoplastic lesions (≥20 mm in size) via conventional EMR is technically difficult, and endoscopic piecemeal mucosal resection (EPMR) is typically applied. Undoubtedly, EPMR is an important method for removing lesions that harbor minimal potential for submucosal invasion, such as intramucosal neoplasms; however, it is crucial to recognize an important disadvantage of EPMR, specifically the increased risk of local recurrence. We previously reported that the removal of more than (or equal to) 5 specimens from a single patient is an independent risk factor for local recurrence following EPMR [25]. Moreover, colonoscopy with careful surveillance is required after multiple EPMR. Given the risk and occurrence of invasive recurrence in EPMR-treated patients, it is advisable to avoid such multiple resections and explore alternative treatment strategies.

4. Endoscopic submucosal dissection

Various treatment materials have been developed and applied in the context of ESD since the introduction of this technique. Hence, we introduce our ESD strategy as an example in this chapter.

4.1. Strategy

4.1.1. Preparation

A well-cleansed colon is a key element of safe ESD in preventing such adverse events such as bacterial peritonitis following iatrogenic perforation of the colonic wall. In our institution, patients generally receive 3 to 4 L of polyethylene glycol over 4 hours in the morning before ESD. Further, they also receive 1 g of cefmetazole in a 100-mL saline solution 20 to 30 minutes prior to ESD.

4.1.2. Sedation

Intravenous administration of an anti-peristaltic agent (10 mg of scopolamine butylbromide or 0.5 mg of glucagon) is mandatory, and intravenous administration of a sedative (2–3 mg of midazolam) and analgesic (15 mg of pentazocine) is provided as required during the procedure. Maintenance of conscious sedation during the procedure is essential, as patients are occasionally required to change position to enable the dissected part of the lesion to hang down due to gravity to improve identification of the submucosal layer.

4.1.3. Treatment devices

Here, we describe the equipment that is commonly used at our institution. ESD is done using a water jet endoscope (PCF-Q260JI and GIF-Q260J, Olympus Medical System Co., Tokyo, Japan). In cases in which handling the endoscope as the operator intended during the ESD

procedure would be difficult due to the location of the lesion or paradoxical movements, a double-balloon colonoscope (EC-450BI, Fujifilm, Japan) is an available option for precise endoscope control [26].

A ball-tip bipolar needle knife with a water jet (Jet B knife, XEMEX Co., Tokyo, Japan) is used for both incision of the mucosa and dissection of the submucosa in the first step of the treatment. An important feature of this device is its use of a bipolar current system, which minimizes damage to deep tissue and decreases perforation risk [27]. Next, an insulation-tipped electrosurgical knife (IT knife nano, KD-612Q, Olympus Optical Co., Tokyo, Japan), fitted with a smaller insulation tip and short blade designed as a small disk to reduce burning of the muscular layer, is usually used to shorten the procedure time [28].

For distal attachment, we use a short-type ST hood (DH-28GR and 29CR, Fujifilm Medical Co., Tokyo, Japan) that facilitates broadening of the visual field of the operator and dissection of the submucosal layer due to its characteristic tapered configuration.

4.1.3.1. Electrosurgical current generator

The ERBE VIO 300 D (Erbe, Tubingen, Germany) is mainly used in our institution. Table 1 describes the output settings for ESD procedures.

	Device	Cut mode [E: effect]	Coagulation mode [E: effect]
Mucosal incision	Jet B knife	Dry Cut, [E]3 100 W	
Submucosal dissection	Jet B knife	Dry Cut, [E]3 100 W	Forced Coag, [E]2 50 W
	IT knife nano	Dry Cut, [E]3 100 W	Swift Coag, [E]2 50 W
Hemostasis	Hemostat-Y		Bipolar, [E]5 25 W

Table 1. Output setting of VIO 300D for colorectal ESD at the National Cancer Center Hospital, Tokyo, Japan

4.1.3.2. Submucosal injection

ESD procedures are critically dependent on the maintenance of suitable submucosal elevation by injection. We therefore prefer solutions for submucosal injection which enable a longer period of submucosal elevation. Two solutions are used in our center, as follows: glyceol (10% glycerin and 5% fructose; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) mixed with small quantities of indigocarmine and epinephrine, and a 0.4% sodium hyaluronate solution (MucoUp; Seikagaku Corp, Tokyo, Japan) [29]. In practice, a small amount of Glyceol is first injected into the submucosal layer to confirm the appropriate submucosal layer elevation; MucoUp is subsequently injected into the properly elevated submucosal layer, after which an additional small amount of Glyceol is injected to flush any residual of MucoUp [30].

http://dx.doi.org/10.5772/60760

4.1.4. Carbon dioxide insufflation

Carbon dioxide (CO_2) gas should be used for colonic lumen insufflation, as previously confirmed [31, 32]. CO_2 insufflation reduces the risk of pneumoperitoneum in cases of perforation, and also reduces the development of abdominal conditions pre- or post-treatment (or both).

4.1.5. ESD technique

In this section, the key points of the ESD technique performed at our institution are described (Figure 3).

The process begins in the retroflex view because endoscope handling can be better stabilized than is achievable with the forward view. After ensuring suitable submucosal elevation via injection, the initial mucosal incision is produced with the Jet B knife from the lesion's distal aspect.

In cases where a retroflex view is difficult to obtain, the tunneling method described by Yamamoto is a useful approach [33]. Briefly, incision and trimming of the mucosa are commenced from the distal aspect of the lesion until the last tissue segment is approached. Incision of the mucosa and dissection of the submucosa are then continued from the lesion's proximal aspect.

In most cases, insertion of the tip of the endoscope into the submucosal layer immediately after the initial mucosal incision is difficult. For these, trimming of the mucosa is performed. As the space for dissection is inadequate for continuation of submucosal dissection during trimming, the submucosal layer is gently and carefully cut near the mucosal layer.

Once the submucosal layer is secure in the visual field, submucosal dissection is furthered with the Jet B knife. One advantage of ESD is the clear visualization of structures in the submucosal layer, such as vessels and fibrosis. This allows the prevention of bleeding by pre-coagulation of the involved vessels. Cutting devices are used to perform pre-coagulation for thin-walled vessels; for thick-walled or pulsatile vessels, however, coagulation forceps should be used. In our center, we use Hemostat-Y forceps (H-S2518, Pentax Co., Tokyo, Japan) in bipolar mode (25 W) for the control of visible bleeding and minimization of any risk of burning of the muscle layer. In ESD, adjustment of the cutting line during submucosal dissection is also possible. In adenomatous lesions, the line of incision can be located near the mucosal layer to minimize perforation risk. In contrast, for potentially submucosal invasive cancer-type lesions, which require R0 resection, the line of incision should be located in the deeper tissues, for example near the muscularis propria, notwithstanding that the risk of perforation is increased.

Once an adequate visual field has been obtained as described, dissection is continued using the IT knife nano. The usable section of this "blade"-type knife is longer than that of other "needle"-type knives and can therefore reduce procedure time compared to those done without this knife. During the entire procedure, submucosal injection should be repeated whenever necessary to ensure suitable submucosal elevation.

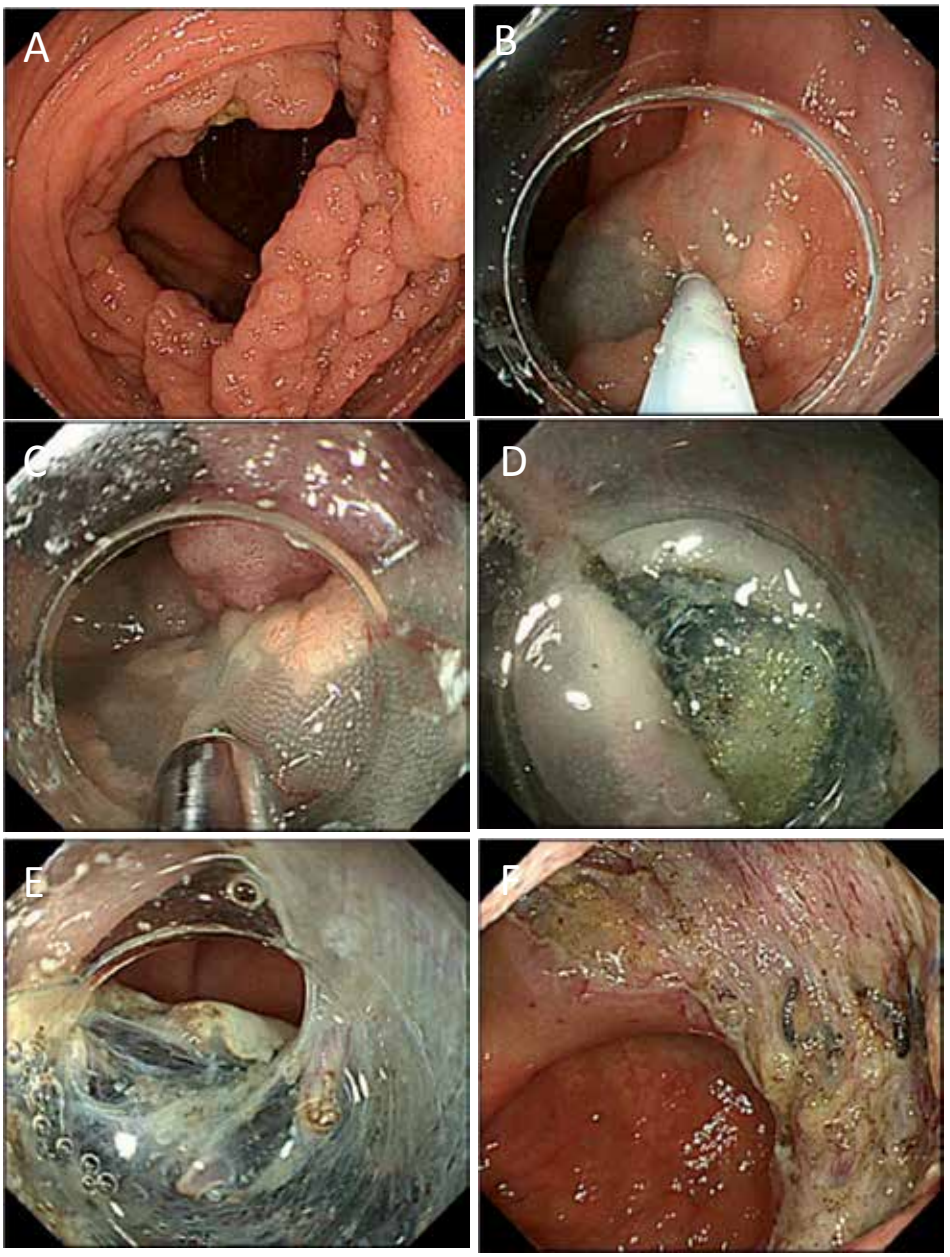

Figure 3. A case of ESD performance. A: Flat elevated lesion (85 mm) located in the ascending colon. It was impossible to maintain the retroflex view for this lesion. B, C: The submucosal injection of glyceol and first circumferential incision were initiated from the oral side of the lesion with a forward view. The first cut was made with a Jet B knife. D: After the first circumferential incision, it was difficult to slide the top of the short-type ST hood into the submucosal layer. Next, the visual field was broadened by carefully cutting the blue-colored submucosal layer near the mucosa (white dotted line). E: After step D, the top of the short-type ST hood slid easily into the submucosal layer, which became easier to cut. Here, the IT knife nano was useful and easily and quickly dissected the submucosal layer. F: En bloc resection was achieved without any adverse events during a period of 180 minutes.

http://dx.doi.org/10.5772/60760

Following the completion of colorectal ESD, a routine colonoscopic review is done to identify possible perforations or exposed vessels, and minimum coagulation is conducted with hemostat-Y forceps on visible but non-bleeding vessels to minimize the risk of bleeding after the operation.

4.2. Alternative technique

Hybrid ESD, which was first reported as "endoscopic resection with local injection of hypertonic saline–epinephrine" by Hirao et al. in 1986, is considered an alternative to ESD. This procedure could enable en bloc resection or at least reduce the number of piecemeal resections for large colorectal neoplasms in a manner that is both safe and relatively rapid. The technique is simple; the first step is a circumferential incision of the mucosa, followed by placement of a snare around the mucosa via the circumferential incision, and tightening of the snare (Figure 3) [34, 35]. However, there are some limitations associated with this technique. From our limited experience, lesions of size more than (or equal to) 35 mm and LST-NG pseudo-depressed–type tumors are often difficult to treat via en bloc resection, and we consider hybrid ESD to be most suitable for lesions measuring 20 to 30 mm.

4.3. Outcomes

In Japan, The Japan Society for Cancer of the Colon and Rectum conducted a multicenter observation study of all patients treated via conventional endoscopic resection and ESD for colorectal neoplasms of size more than 20 mm from October 2007 to December 2010 [36]. A total of 816 lesions were treated via ESD, and the short-term outcomes were as follows. The mean lesion diameter was approximately 40 mm. En bloc resection was achieved in more than 90% of cases regardless of lesion size, with a perforation rate of 2.0% and delayed bleeding rate of 2.2%. No perforation cases required emergency surgery and all were treated conservatively by endoscopic closure; nothing per os, antibacterial therapy. Hence, most iatrogenic perforations are very small and can be closed by endoscopic clip placement.

4.4. Training for ESD

Given the high risk of complications that arise from the anatomical characteristics of the colon, ESD requires a high level of skill and experience in endoscopy. A better understanding of the learning curve for ESD is therefore required to standardize training, and to achieve a more global acceptance of this technique. At our institution, endoscopists who will begin using ESD must meet the following prerequisites to perform colorectal ESD: a high level of skill in the non-loop insertion colonoscopy technique (more than 10 cases of total colonoscopy completed within 5 minutes without any abdominal discomfort), skill in conventional EMR or EPMR techniques, experience with more than 20 gastric ESD cases, and assistance in more than 20 colorectal ESDs conducted by experienced endoscopists [37]. In Western countries, however, gastric cancer is less common than colorectal cancer, and the introduction of trainees to ESD using colorectal lesion resection as a first step might be difficult. When required, trainees should start clinical training in colorectal ESD with lower rectal lesions, which carry a lower risk of perforation and a similar setting to gastric lesions.

We reported the short-term outcomes of colorectal ESD performed by less-experienced endoscopists [37, 38]. In terms of the learning curve, the endoscopists could perform the technique safely and independently after preparatory training and experience of 30 or more cases. On the other hand, most LST-G tumors of size less than (or equal to) 40 mm could be treated safely within a 120-minute procedure time without any adverse events. Therefore, we recommend that an LST-G tumor of size less than 40 mm is likely suitable for introducing trainees to ESD.

5. Conclusion

Various treatment materials have been developed and applied to ESD since the introduction of this technique. Of note, ESD is reliable for the en bloc resection of large colorectal superficial neoplasms. It has a better success rate than EPMR and enables more accurate pathological evaluations. In addition, colorectal ESD reduces unwanted surgery for mucosal carcinomas and improves the overall quality of life of patients with lesions in the lower rectum. Nevertheless, the technical difficulty of ESD and the complications associated with it, including iatrogenic perforation, have held back its wider global adoption. We consider that adoption of this technique will improve in future following further development of treatment devices with improved safety and reduced technical difficulty. However, there is no exact standardized procedure for ESD, and it is important to continue efforts toward improving the safety and technical ease of the procedure.

Author details

Taku Sakamoto*, Masayoshi Yamada, Takeshi Nakajima, Takahisa Matsuda and Yutaka Saito

*Address all correspondence to: tasakamo@ncc.go.jp

Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

References

[1] Morson BC, Whiteway JE, Jonse EA, et al. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. Gut. 1984;25:437-444.

[2] Fujimori T, Kawamata H, Kashida H. Precancerous lesion of the colorectum. J Gastroenterol. 2001;36:587-594.

[3] Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology. 2013;144:551-559.

[4] Sakamoto T, Matsuda T, Nakajima T, et al. Clinicopathological features of colorectal polyps: Evaluation of the 'predict, resect and discard' strategies. Colorectal Dis. 2013;15(6):e295-e300.

[5] Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: A case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc. 2007;66:966-973.

[6] Fujishiro M, Yahagi N, Kakushima N, et al. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol. 2007;5:678-683.

[7] Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: Possibility of standardization. Gastrointest Endosc. 2007;66:100-107.

[8] Saito Y, Uraoka T, Yamaguchi Y, et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc. 2010;72:1217-1225.

[9] Ikematsu H, Matsuda T, Emura F, et al. Efficacy of capillary pattern type IIIA/ IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. BMC Gastroenterol. 2010;10:33.

[10] Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: Validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc. 2013;78:625-632.

[11] Matsuda T, Fujii T, Saito Y, et al. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol. 2008;103:2700-2706.

[12] Uraoka T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut. 2006;55:1592-1597.

[13] Matsuda T, Parra-Blanco A, Saito Y, et al. Assessment of likelihood of submucosal invasion in non-polypoid colorectal neoplasms. Gastrointest Endosc Clin N Am. 2010;20:487-496.

[14] Sakamoto T, Saito Y, Nakajima T, et al. Comparison of magnifying chromoendoscopy and narrow-band imaging in estimation of early colorectal cancer invasion depth: A pilot study. Dig Endosc. 2011;23:118-123.

[15] Tobaru T, Mitsuyama K, Tsuruta O, et al. Sub-classification of type VI pit patterns in colorectal tumors: Relation to the depth of tumor invasion. Int J Oncol. 2008;33:503-508.

[16] Saitoh Y, Obara T, Einami K, et al. Efficacy of high-frequency ultrasound probes for the preoperative staging of invasion depth in flat and depressed colorectal tumors. Gastrointest Endosc. 1996;44:34-39.

[17] Turuta O, Kawano H, Fujita M, et al. Usefulness of the high-frequency ultrasound probe in pretherapeutic staging of superficial-type colorectal tumours. Int J Oncol. 1998;13:677-684.

[18] Hurlstone DP, Brown S, Cross SS, et al. High magnification chromoscopic colonoscopy or high frequency 20 MHz mini probe endoscopic ultrasound staging for early colorectal neoplasia: A comparative prospective analysis. Gut. 2005;54:1585-1589.

[19] Matsumoto T, Hizawa K, Esaki M, et al. Comparison of EUS and magnifying colonoscope for assessment of small colorectal cancers. Gastrointest Endosc. 2002;56:354-360.

[20] Fu KI, Kato S, Sano Y, et al. Staging of early colorectal cancers: Magnifying colonoscopy versus endoscopic ultrasonography for estimation of depth of invasion. Dig Dis Sci. 2007;53:1886-1892.

[21] Uno Y, Munakata A. The non-lifting sign of invasive colon cancer. Gastrointest Endosc. 1994;40:485-489.

[22] Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology. 2011;140:1909-1918.

[23] Kobayashi N, Saito Y, Sano Y, et al. Determining the treatment strategy for colorectal neoplastic lesions: Endoscopic assessment or the non-lifting sign for diagnosing invasion depth? Endoscopy. 2007;39:701-705.

[24] Saito Y, Kawano H, Takeuchi Y, et al. Current status of colorectal endoscopic submucosal dissection in Japan and other Asian countries: Progressing towards technical standardization. Dig Endosc. 2012;24 Suppl 1:67-72.

[25] Sakamoto T, Matsuda T, Otake Y, Nakajima T, Saito Y. Predictive factors of local recurrence after endoscopic piecemeal mucosal resection. J Gastroenterol. 2012;47:635-640.

[26] Ohya T, Ohata K, Sumiyama K, et al. Balloon overtube-guided colorectal endoscopic submucosal dissection. World J Gastroenterol. 2009;15:6086-6090.

[27] Nonaka S, Saito Y, Fukunaga S, et al. Impact of endoscopic submucosal dissection knife on risk of perforation with an animal model-monopolar needle knife and with a bipolar needle knife. Dig Endosc. 2012;24:381.

[28] Hotta K, Yamaguchi Y, Saito Y, Takao T, Ono H. Current opinions for endoscopic submucosal dissection for colorectal tumors from our experiences: Indications, technical aspects and complications. Dig Endosc. 2012;24 Suppl 1:110-116.

[29] Uraoka T, Fujii T, Saito Y, et al. Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc. 2005;61:736-740.

[30] Yamamoto H, Kawata H, Sunada K, et al. Successful en bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy. 2003;35:690-694.

[31] Saito Y, Uraoka T, Matsuda T, et al. A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. Gastrointest Endosc. 2007;65:537-542.

[32] Kikuchi T, Fu KI, Saito Y, et al. Transcutaneous monitoring of partial pressure of carbon dioxide during endoscopic submucosal dissection of early colorectal neoplasia with carbon dioxide insufflation: A prospective study. Surg Endosc. 2010;24:2231-2235.

[33] Monkemuller K, Wilcox CM, Munoz-Navas M, eds. Interventional and Therapeutic Gastrointestinal Endoscopy. Front Gastrointest Res. Basel; Karger; 2010. Vol 27, pp 287-295.

[34] Terasaki M, Tanaka S, Oka S, et al. Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. J Gastroenterol Hepatol. 2012;27:734-740.

[35] Sakamoto T, Matsuda T, Nakajima T, et al. Efficacy of endoscopic mucosal resection with circumferential incision for patients with large colorectal tumors. Clin Gastroenterol Hepatol. 2012;10:22-26.

[36] Nakajima T, Saito Y, Tanaka S, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc. 2013;27:3262-3270.

[37] Sakamoto T, Saito Y, Fukunaga S, et al. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. Dis Colon Rectum. 2011;54:1307-1312.

[38] Sakamoto T, Sato C, Makazu M, et al. Short-term outcomes of colorectal endoscopic submucosal dissection performed by trainees. Digestion. 2014;89:37-42.

Chapter 8

Endoscopic Treatment of Pancreatic Diseases

Borislav Vladimirov, Plamen Getzov and
Radina Ivanova

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60589

Abstract

Endoscopic therapy has been increasingly recognized as an effective method of treatment in selected patients with pancreatic diseases. Various endoscopic procedures, classical and modified, are used for the complex treatment of acute and chronic pancreatitis, as well as their complications. In pancreatic carcinoma, some endoscopic methods are applied mainly as palliative measures. There are still open questions regarding the placing and timing of various endoscopic procedures in the multidisciplinary management approach of pancreatic diseases.

Keywords: endoscopy, EUS, acute pancreatitis, pancreatic cancer

1. Introduction

Acute pancreatitis (AP) is a disease with multiple etiologies and an increasing incidence, showing a wide spectrum of outcomes – from a mild, self-limited to severe, life-threatening illness [1]. According to the revised Atlanta classification of 2012, AP can be either edematous interstitial pancreatitis or necrotizing pancreatitis, involving necrosis of the peripancreatic tissues and/or pancreatic parenchyma [2]. In AP, there are 3 degrees of severity: mild, moderate, and severe – mild AP lacks both organ failure and local complications; moderately severe AP has transient organ failure (<2 days), local complications, and/or exacerbation of a coexistent disease; and severe AP is defined by the presence of persistent organ failure (≥2 days). Local complications are classified according to the presence of fluid or solid (necrosis) component as acute peripancreatic fluid collections, pseudocysts, acute (pancreatic/peri-

pancreatic) necrotic collection, and walled-off necrosis. Acute peripancreatic fluid collection is a true fluid collection that develops in the early phase of interstitial edematous AP, lacks a wall, and usually resolves without intervention. Pancreatic pseudocysts (PPC) are encapsulated collections of fluid with a well-defined inflammatory wall and with minimal or no necrosis, which usually occurs more than 4 weeks after onset of AP. Acute necrotic collections (ANCs) are present in the first 4 weeks of the necrotizing AP and contain variable amounts of solid (necrotic) and fluid material secondary to pancreatic and/or peripancreatic necrosis. Walled-off pancreatic necrosis (WOPN) represents the mature phase of an ANC, confined by a wall of reactive tissue which develops usually 4 or more weeks after the onset of necrotizing disease. Both ANCs or WOPN can be sterile or infected. Severe AP is estimated to occur in up to 20% of patients and is associated with high morbidity and mortality (approximately 15%) due to the development of sterile or infected necrosis, sepsis, and progressive multisystem organ failure [3, 4]. Development of infected necrosis is observed in 25%–70% of patients with necrotizing disease and usually requires an intervention to control the sepsis [5, 6]. Currently, endoscopic therapy, including various endoscopic procedures, is a part of multidisciplinary management of AP. It is indicated as a minimal invasive method of therapy in selected cases with acute biliary pancreatitis and local complications of AP. In addition, pancreatic endotherapy has been demonstrated to be effective in selected cases of idiopathic AP.

1.1. Endoscopic management in acute biliary pancreatitis

The most common cause of AP is gallstones. In most of the patients presenting with acute biliary pancreatitis the gallstones pass spontaneously to the duodenum but in minority of patients (about 20%) the persistent biliary obstruction can lead to cholangitis and severe AP [1]. The duration of bile duct obstruction is an important contributing factor for the severity of AP. It was reported that pancreatic necrosis develops more often when the biliary obstruction exceeds 48 h [7]. In the past, urgent surgery to decompress the bile duct soon after the diagnosis of pancreatitis was associated with increased mortality [8, 9]. Endoscopic retrograde cholangiopancreatography (ERCP) is a less invasive method to clear the bile duct and it could favorably affect the clinical outcome of AP if utilized properly [10, 11]. It is generally accepted that early ERCP and endoscopic sphincterotomy (ES) are indicated in cases with acute cholangitis and obstructive jaundice [12, 13]. In such patients, early ERCP and ES, preferably within 72 h from the onset of AP, ameliorate the symptoms and the progression of AP [14]. There is no clear consensus on the benefit from the endoscopic approach in patients with ERCP in patients with elevated liver function tests and obstructive jaundice with a septic-appearing picture and severe disease graded by an accepted scoring system. The role and timing of ERCP in patients with acute biliary pancreatitis have been evaluated in a number of clinical trials and meta-analysis (Figure 1) [12, 13, 15-23]. The authors of the first study found that patients with predicted severe biliary pancreatitis (using modified Glasgow criteria) had fewer complications if they underwent ERCP within 72 h (24% vs 61%) compared to the control group on conservative management [15]. After excluding the patients with concomitant acute cholangitis (the most probable to benefit from early ERCP), the difference remained (15% vs 60%). Similar results were reported in another randomized study, in which the ERCP was performed within 24 h after admission [12]. The early ERCP group with predicted severe

http://dx.doi.org/10.5772/60589

pancreatitis had fewer complications (13% vs 54%) compared to the patients group on conservative treatment. One multicenter study evaluated the benefit of early ERCP in preventing severe AP in patients without acute cholangitis and/or biliary obstruction (serum bilirubin levels < 5 mg / dl) [13]. Their results showed no superiority of early ERCP regarding morbidity and/or mortality in the study group, but also an unusually high mortality (8%) among the patients with predicted mild pancreatitis. The most recent meta-analysis, including 7 randomized trials (n=757), found no evidence that early routine ERCP significantly affects mortality or local/systemic complications, regardless of the predicted severity of biliary pancreatitis, but it should be considered in patients with coexisting cholangitis or biliary obstruction [23]. Among the trials that included patients with cholangitis, the early routine ERCP strategy significantly reduced mortality, local and systemic complications as defined by the Atlanta Classification. Among trials that included patients with biliary obstruction, the early routine ERCP strategy was associated with a significant reduction in local complications as defined by authors of the primary study, but a nonsignificant trend toward reduction of local and systemic complications as defined by the Atlanta Classification. Although accurate prediction of common bile duct stones in acute biliary pancreatitis is warranted to select patients for early therapeutic ERCP, it should be noted that predicting their presence in the early stages of disease with complete liver biochemistry, transabdominal ultrasonography, or CT is unreliable [24]. In cases with severe biliary pancreatitis, the differential diagnosis between acute cholangitis and severe AP with systemic inflammatory response syndrome may be also difficult [10, 11]. In cases with suspected biliary obstruction, magnetic resonance cholangio-pancreatography (MRCP) or endoscopic ultrasound (EUS) when accessible are the preferred diagnostic modalities to identify it [25-28]. In patients with AP, the sensitivity and specificity of EUS and ERCP were the same (96% vs 96% and 85% vs 92%, respectively) for detecting choledocholithiasis [27]. By their use, ERCP would be reserved for patients with strong evidence of obstruction. In 2012, the IAP/APA (International Association of Pancreatology/American Pancreatic Association) evidence-based guidelines for the management of AP has been published [29]. It provides recommendations concerning the key topic on multidisciplinary management of AP. The following recommendations for the management of acute biliary pancreatitis, classified to their GRADE strength (1-strong, 2-weak) and quality of evidence (A - high, B - moderate, C- low) have been given: "ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis. ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis. ERCP is probably indicated in biliary pancreatitis with common bile duct (CBD) obstruction. ERCP is indicated in patients with biliary pancreatitis and cholangitis. Urgent ERCP (<24 h) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis. MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones. MRCP is less invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS.

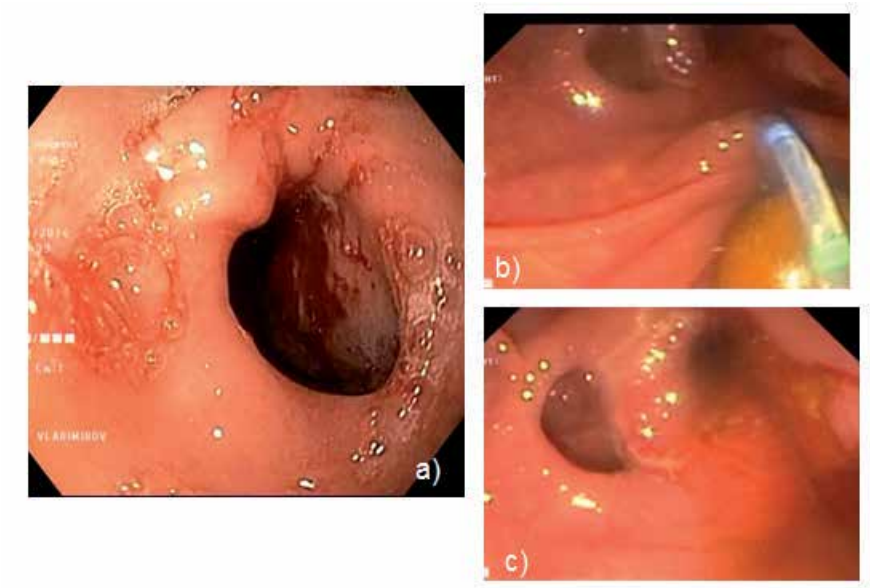

Figure 1. Endoscopic management of acute biliary pancreatitis. a) A view of compression of duodenal wall by enlarged gall bladder. b) Papillary sphincterotomy with extraction of impacted gall stone. c) A periampullary diverticulum neighboring on sphincterotomy.

1.2. Endoscopic management of local complications in AP (pancreatic necrosis/WOPN, PPC, disrupted pancreatic duct)

In the last years, the minimally invasive interventions for management of necrotizing pancreatitis have replaced the traditional open necrosectomy. Laparotomy and immediate surgical debridement of the infected necrotic tissue have been the gold standard treatment for a long time [5, 30]. This concept has been changed by multiple reports showing that early surgical intervention for pancreatic necrosis could result in a worse prognosis compared to cases where surgery is delayed or avoided [31-35]. Besides percutaneous drainage and minimally invasive surgery, endoscopic transmural drainage (ETD) and necrosectomy have an increasing role as an alternative to open surgery. The results of different multicenter studies and randomized trials, as well as systematic reviews, evidence-based guidelines and consensus statements have supported the safety and efficacy of endoscopic and other minimally invasive techniques in the management of severe AP and its complications [1, 29-32, 35-44]. In summary, intervention is primarily indicated for infected necrosis and less often for symptomatic sterile necrosis. They should be delayed 4 weeks or longer after the onset of disease, for better demarcation and liquefaction of the necrosis. Both the step-up approach using percutaneous drainage followed by minimally invasive video-assisted retroperitoneal debridement and endoscopic necrosectomy have been shown to have superior outcomes to traditional open necrosectomy with respect to short-term and long-term morbidity. Applicability of these techniques depends on the availability of specialized expertise and a multidisciplinary team dedicated to the management of severe AP and its complications [38]. According to the guidelines of IAP/APA

http://dx.doi.org/10.5772/60589

(2012), common indications for intervention (either radiological, endoscopical, or surgical) in necrotizing pancreatitis are clinical suspicion or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off [29]. At present, there are insufficient data to define subgroups of patients with suspected or confirmed infected necrotizing pancreatitis who would benefit from a different treatment strategy, but percutaneous catheter or ETD should be the first step in the treatment of these patients, followed by endoscopic or surgical necrosectomy if needed. In the multicenter randomized trial, including 88 patients with infected necrotizing pancreatitis, the Dutch Pancreatitis Study group showed that the step-up approach of percutaneous (retroperitoneal) catheter drainage and followed, if needed, by minimally invasive necrosectomy, decreased major short-term complications (40% vs 70%) and costs as compared to primary open necrosectomy [36]. The rates of late complications as diabetes and exocrine pancreatic insufficiency were also lower in the step-up cohort of patients. Lately published trial by the same group, in which the patients were randomized to endoscopic transgastric versus open necrosectomy, demonstrated a lower rate of proinflammatory response, organ failure, and major complications in patients undergoing EUS-guided necrosectomy as compared to surgical necrosectomy [41]. The results from a currently performed multicenter randomized controlled trial (TENSION trial) comparing endoscopic transluminal to minimally invasive surgical step-up approach are awaited [45]. A small proportion of patients with documented infected necrosis who remain clinically stable can be managed with antibiotics alone, without the need for percutaneous catheter drainage or necrosectomy. Future studies should compare (initial) antibiotic treatment of infected necrosis with other, more invasive, strategies [29]. The vast majority of patients with sterile necrotizing pancreatitis can be managed without intervention. Indications for intervention (either radiological, endoscopical, or surgical) in this group of patients are: ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of WOPN; persistent symptoms ("persistent unwellness") in patients with WOPN without signs of infection; disconnected duct syndrome in the presence of persisting symptomatic collection with necrosis. Rare complications requiring (nonsurgical) intervention in the follow-up after sterile necrotizing pancreatitis are pancreaticopleural fistula, pancreatic ascites, and a "true" (no necrosis found in the collection on MR or ultrasonography) symptomatic pseudocyst.

Several comprehensive reviews discussing indications, timing, standard and novel approaches, outcomes, and complications regarding ETD and necrosectomy in infected necrotizing pancreatitis have been published recently [2, 3, 38, 39, 42-47]. The technique of endoscopic transluminal necrosectomy (ETN) involves a transmural (transgastric or transduodenal) access to the WOPN, followed by large-caliber balloon dilation of the tract between the collection and the gastrointestinal wall, allowing the insertion of an endoscope into the collection to visualize the necrotic material, mechanical debridement, and lavage. A variety of tools, such as baskets, snares, and nets have been used to remove the necrotic tissue. A stent (plastic/metal) is left in place at the end of the procedure to keep the fistula patent and to allow access into the necrotic cavity at a later session. Most patients with severe AP complicated by WOPN require multiple sessions to achieve radiographic and clinical success. One recent systematic review on the ETN of pancreatic necrosis found that a median of 4 (1-35) sessions are needed to achieve resolution of the necrotic collection [42]. EUS-guided necrosectomy is increasingly used due to the ability

of EUS to visualize and determine the optimal access into the collection, to avoid intervening blood vessels, to assess the contents of the cavity, and to visualize bleeding into the collection and other complications during and immediately after the procedure [46]. One recent systematic review reported that EUS-guided necrosectomy has been performed in 283 published cases so far [48]. Currently used endoscopic accessories during ETN are designed for other purposes and are not optimal in achieving adequate necrotic debridement in a limited time. The authors of one study showed that drainage of necrotic collections with multiple instead of a single transmural access, placing multiple stents and a nasocystic drainage in each tract (multiple transluminal gateway technique), led to better long-term clinical outcomes [49]. Other authors reported that the use of hydrogen peroxide in their small case series facilitates the removal of necrotic debris, but the benefit and potential complications need to be further investigated [50, 51]. The use of metal stents specially designed for drainage of pancreatic fluid collections was also reported in small case studies and the results regarding their efficacy are awaited [52-54].

The summary results of various studies show that ETN is an effective minimally invasive treatment in infected necrotizing pancreatitis. It was reported that the success rate of peroral endoscopic drainage/debridement of WOPN was 81% of 53 studied patients [55]. Results from a multicenter US series demonstrated a resolution rate of 91% (95/104 patients with WOPN) as the mean time to resolution was 4.1 mo from the initial procedure [56]. A recent systematic review, including 15 studies (455 patients), reported that with ETN definitive successful treatment was achieved in 81% of patients, mortality was 6%, and complications occurred in 36% of patients [44]. Bleeding was the most common complication (18%), following perforations to the peritoneum. Other reported complications included infection, aspiration, stent migration, occlusion, pancreatic duct damage, complications of sedation, and gas embolism. In the systematic review on EUS-guided necrosectomy, it was found that the mean technical and clinical success rates were 100% and 88%, respectively; mean overall complication rate was 28%, and mean overall recurrence rate was 7% [48]. The results of one recently published systematic review and meta-analysis of ETN for WOPN (8 studies) showed that the mean time of ETN after onset of AP was 7 weeks; the mean size of the necrotic cavity was 12.87 cm and the weighted mean number of endoscopic procedures needed to resolve the necrotic cavity was 4.09 [43]. The pooled proportion of successful resolution of pancreatic necrosis using ETN was 81.84% and that of recurrence after ETN was 10.88%. Complications were noted in 21.33% of patients, including bleeding, sepsis, and perforation. For pancreatic necrosis that did not resolve, surgery was performed in 12.98% of patients. The authors of this meta-analysis conclude that ETN is safe and effective at treating patients with symptomatic WOPN and offers the advantage of minimally invasive endoscopic treatment without transabdominal surgery but better techniques and equipment are still needed to improve procedural efficiency. The decisions to perform ETN should be made by advanced endoscopists in collaboration with a multidisciplinary team with the facilities and personnel to manage these complex patients.

Symptomatic pancreatic pseudocysts (abdominal pain, gastric outlet, obstructive jaundice) and disrupted pancreatic duct in AP are also indicated for endoscopic therapy. The literature data show that the incidence of APFC in acute edematous pancreatitis is around 40% and development of PPC is approximately 10% of these cases [57]. Earlier it had been

http://dx.doi.org/10.5772/60589

reported that pseudocysts result from pancreatic duct disruption in up to 10%–25% of cases with AP and in 20%–40% of chronic pancreatitis (CP) cases [58]. Endoscopic drainage of PPC (transpapillary, transmural, or combination of the both) has been demonstrated as effective minimally invasive method for their treatment in a number of studies. The results regarding technical success, recurrence, and complications rates will be discussed below, in endoscopic therapy of PPC in CP.

Disruption of the pancreatic duct (PD) secondary to pancreatic necrosis occurs in attacks of AP and leads to leakage of the pancreatic secretion and its accumulation inside the abdomen in the neighborhood of the pancreas and pseudocyst formation [4]. It may also result in pancreatic ascites or pancreatic fistulae. Endoscopic treatment of the disrupted PD includes transpapillary stent bridging of the pancreatic leak or diverting pancreatic duct flow [59]. The efficacy of these techniques has been demonstrated in several studies [60-62]. Complete duct disruptions are refractory to transpapillary stenting because the upstream disconnected segment maintains secretion. Therefore, ETD has arisen as the procedure of choice for cases with complete duct disruptions [62].

1.3. Endoscopic therapy in idiopathic acute pancreatitis

Idiopathic AP is defined as pancreatitis with no etiology established after initial laboratory and imaging tests (transabdominal ultrasound and CT in the appropriate patient) [63]. Patients with idiopathic AP should be evaluated at specialized centers on pancreatic diseases, applying combined multidisciplinary approach, including advanced endoscopy [1]. Various anatomic (pancreas divisum, anomalous anomalous pancreatobiliary duct junction, choledochal cysts/choledochocele, periampullarry diverticulae, ampullary tumors) and physiologic anomalies (sphincter of Oddi dysfunction/SOD) can contribute to recurrent episodes of AP and many of them can often be diagnosed and treated endoscopically [3, 64, 65]. The diagnostic role of ERCP can help define specific causative factors in patients with idiopathic AP, but its major limitation is the risk of post-ERCP pancreatitis, which varies from 5% to 10% and reaches 30% in cases with SOD. For this reason, diagnostic and therapeutic endoscopy in these cases should be performed in specialized units.

Pancreas divisum (PD) is reported in about 20% of patients with acute recurrent pancreatitis [65]. Endoscopic therapy in PD includes minor papilla sphincterotomy, papillary dilation, stent placement, or a combination of these techniques. Endoscopic and surgical therapy are comparably effective in 70%-90% of patients with PD but endoscopic therapy as minimally invasive method is preferred in most cases [66]. In patients with dilated dorsal duct or abnormal function test, and no ductal strictures upstream of the minor papilla, sphincterotomy is the procedure of choice. A short-term dorsal pancreatic duct stent placement is recommended to avoid postprocedure complications. Although endoscopic therapy has been proved effective in a large percentage of cases with PD, there is only one small randomized controlled trial [67]. The authors reported that in the treatment group, 9 out of 10 patients (90%) had no further episodes of AP during a 3-year follow-up, while 6 of 9 patients (67%) who were randomized to no treatment had at least one episode.

Endoscopic management, including biliary sphincterotomy alone, is also the method of choice for patients with uncomplicated type 3 choledochal cyst/choledochoceles. Treatment of most other choledochal cysts is mostly surgical because for their potential of malignant degeneration [3]. The presence of periampullary diverticulum, although rarely, can also be a cause for acute relapsing pancreatitis. Endoscopic sphincterotomy in a small series of patients was found to be effective with no further episodes of AP during the follow-up period [68]. It has been estimated that 5%–14% of patients with benign or malignant pancreatobiliary tumors present with idiopathic AP [69-72]. Pancreatic cancer should be suspected in any patient >40 years of age with idiopathic pancreatitis, especially those with a prolonged or recurrent course [72]. Ampullary tumors can be resected either surgically or endoscopically [3]. It was reported that endoscopic treatment (snare polypectomy with sphincterotomy) was successful in the removal of ampullary tumors with no ductal invasion in up to 90% of cases [73, 74]. Procedure-related pancreatitis could be reduced by prophylactic stent placement and a long-term surveillance with endoscopic biopsies was recommended.

Sphincter of Oddi dysfunction is a nonmalignant condition resulting in impairment in sphincteric physiology, leading to outflow obstruction. SOD is reported in about one-third of cases with recurrent pancreatitis [65]. The diagnosis is confirmed by endoscopic SO manometry. In documented SOD, endoscopic therapy includes biliary and/or pancreatic sphincterotomy. Prophylactic pancreatic stenting for two weeks after sphincterotomy has shown to reduce the incidence of post-ERCP pancreatitis [75]. Clinical improvement after sphincterotomy has been reported in 55%–95% of patients, depending on the type of SOD, and manometric recordings [76, 77]. The analyses of published studies (237 patients with follow-up ranging from a mean of 3 months to 5 years) showed that favorable outcomes are the highest in type I SOD cases (83%–100%) while in type II SOD patients long-term symptom relief was reported in up to 79%, depending on whether manometry was abnormal. One recent study, including 69 patients with recurrent AP and pancreatic SOD randomized to biliary sphincterotomy with and without pancreatic sphincterotomy showed that the recurrence of pancreatitis was similar in both groups (48.5% vs 47.2%) [78].

2. Endoscopic therapy in chronic pancreatitis

In recent years with advances in technology, endoscopic therapy is one effective management option in CP along with medical and surgical treatments. Endoscopy became preferable management in selected patients with CP because of high success rate and low morbidity and mortality. The results are comparable to surgery [79-82]. In addition, the procedure may be repeated with no extra risk [83]. Endoscopic therapy may reduce or eliminate the need for surgical procedures, may serve as a bridge to surgery in poor operative candidates, and can predict the response to surgical therapy [84-85]. If endoscopic therapy is unsuccessful, surgical therapy is still a potential option for most patients.

Today endoscopic therapy is performed in patients with CP who are unlikely to respond or have failed medical therapy, or when it is necessary to resort to long-term opioid administra-

http://dx.doi.org/10.5772/60589

tion [83, 86-89]. The aims of endoscopic therapy in CP are to relieve outflow obstruction of main pancreatic duct (MPD) to control of pain, as well as to manage complications such as ductal strictures, calculi, pseudocysts, and biliary strictures [83, 86-90]. Endoscopic therapy is based on different techniques and procedures, such as ERCP, pancreatic sphincterotomy, pancreatic stones extraction, pancreatic and biliary stenting, and drainage of pseudocysts. Extracorporeal shockwave lithotripsy (ESWL) for MPD stones may be combined with endoscopic procedures. Advances in EUS have improved PPC drainage and cannulation of inaccessible MPD, as well as celiac plexus block [83, 86, 87, 89].

We evaluated the endoscopic methods of therapy in patients with CP (n=114, group), and compared the results to those of control group of patients, treated by conventional conservative methods (n=100, group) [91]. All cases were followed-up for a period of 3 years. The early and late results showed that endoscopic treatment led to clearance of common pancreatic duct by stone extraction (82% and 71%), control of strictures/fistulae by stenting (76% and 68%), (Figure 2), and pseudocyst decompression by cystogastrostomy under EUS plus dilation and stenting (73% and 30%), (Figure 3). Symptoms improvement, especially pain, was observed in 86% versus 17% (6th month) and 70% versus 14% (3rd year) in group and group , respectively ($p<0.001$). Endoscopic treatment significantly reduced the incidence of new pancreatic attack ($p<0.01$). New formation of pancreatic duct stones occurred in 2/17 patients. Replacement of pancreatic prostheses was needed in 41%. New ductal or parenchymal changes were observed in 25%. According to these data we suggest that endoscopic procedures are one alternative strategy in chronic pancreatitis with impaired drainage, leading to pancreatic duct or pseudocysts drainage, reductions of pain and incidence of pancreatic attack, but recurrent and complications rates are higher.

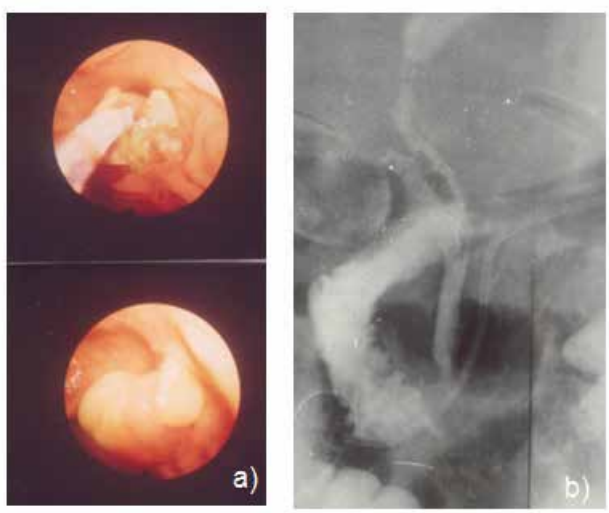

Figure 2. a, b) Endoscopic therapy in CP- insertion of endoprosthesis in a case with pancreatic ductal stricture.

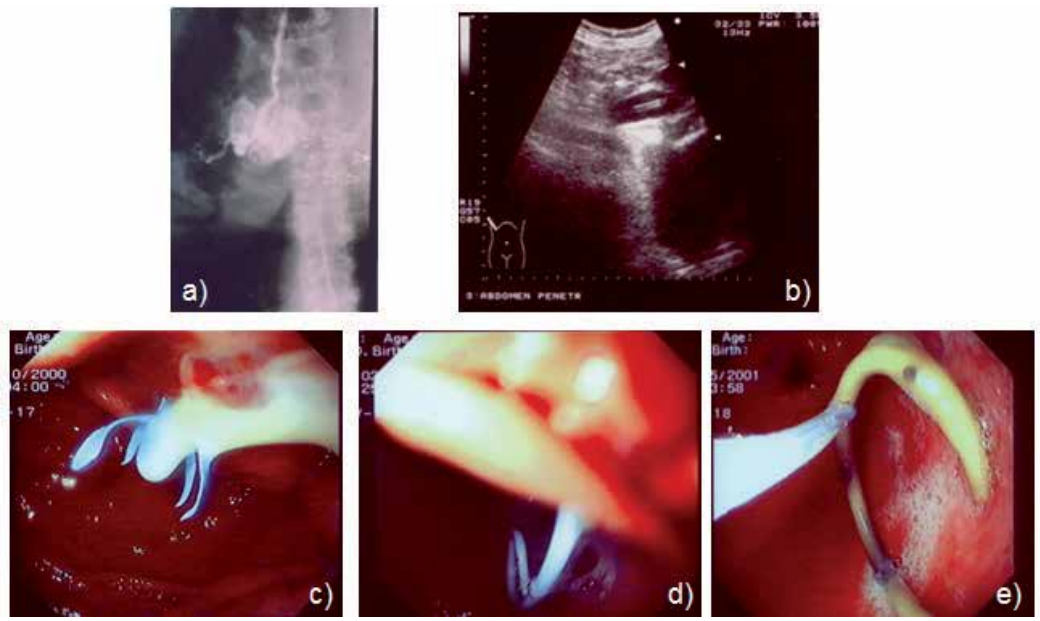

Figure 3. a, b, c, d, e) EUS-guided transgastric drainage of pancreatic pseudocyst in a case with CP.

In the last 10 years, there are accumulating data for the utility of endoscopic therapy and its efficacy and limitations in various painful conditions and complications associated with CP.

2.1. Painful uncomplicated CP

In the last version of the European Society of Gastrointestinal Endoscopy (ESGE) Guideline [86] on endoscopic treatment of painful uncomplicated CP, the following recommendations are given:

"Endoscopic therapy is the first-line therapy for painful uncomplicated CP. The clinical response should be evaluated at 6–8 weeks. If it appears unsatisfactory, the patient's case should be discussed again in a multidisciplinary team with endoscopists, surgeons, and radiologists and surgical options should be considered, in particular in patients with a predicted poor outcome following endoscopic therapy" (*Recommendation grade B).*

Randomized controlled clinical trials comparing endoscopic and surgical pain treatment in CP showed better results for surgery [92-94]. In [92], it was reported that pain relief was 15% for endoscopic therapy versus 34% for surgery after 5 years of follow-up. It has been discussed that these results showed that neither of these options is satisfactory, and also that endoscopic therapy was not optimal [86]. ESWL and cumulative stenting were not used, and endoscopic therapy was not repeated in the case of recurring symptoms. In the trials of [93, 94], the initial stenting period was relatively short as stents were removed when the stricture had disappeared on the pancreatogram, but recurrence was observed when pain and stricture persisted. This is in contrast to most other studies, in which stenting is continued for 1–2 years. In

http://dx.doi.org/10.5772/60589

addition, included were patients with advanced disease with strictures and stones, as well as opioid-dependence. For these reasons, the results cannot be extrapolated to all patients with CP [86]. The long-term follow-up after endoscopic therapy in a total of 1890 patients with CP showed that 83% of them had no need of pancreatic surgery [82, 95-99]. In addition, surgery was associated with higher morbidity (18%–53%) and mortality (0%–5%) in comparison with endoscopic therapy of CP (3%–9% morbidity and 0%–4% mortality) [82, 100-103]. Pain relief was observed in 70%–94% of patients in the short-term followed-up, and in 52%–82% of patients in the long-term followed-up endoscopic treatment [104-108]. Similar results of endoscopic decompression therapy were found in patients with all types of obstruction, including calculi alone, stenosis alone, or a combination of both [87, 104]. After endotherapy, the number of pain-related hospitalizations and the need for analgesics decreased, but patients' quality of life was not improved significantly [89, 96, 109]. According to the Spanish Pancreatic Club's recommendations for the diagnosis and treatment of CP, endoscopic decompression treatment is less effective and has shorter-term effects compared to surgery [88]. Endoscopic pain treatment has been shown to be effective for patients with a dilated MPD, particularly when various endoscopic techniques are combined [88, 89]. Reference [88] shows also some limitations of endoscopic treatment. Better pain control following surgery compared to endoscopic therapy was observed in randomized clinical trials, but both endoscopic and surgical therapy had been tested in a randomized trial versus medical therapy. It is difficult to assess pain control of endoscopic therapy in long-term studies without a control group, given the tendency of its decreasing effects over time. Finally, endotherapy is a technically difficult and an operator-dependent procedure. ESGE experts [86] have shown some factors independently associated with long-term (≥2 years) successful endoscopic pain relief. These factors include: the obstructive calcifications in the head of the pancreas; short disease duration and low frequency of pain attacks before endoscopic therapy; complete MPD stone clearance; absence of MPD stricture at initial endoscopic therapy; and discontinuation of alcohol and tobacco during follow-up [96, 97, 99, 110-111].

In a painful CP with minimal or no ductal change with absence of ductal strictures or stones **(**mild CP according to Cambridge classification), endoscopic pancreatic sphincterotomy (EPS) is a method of therapy and it offers symptomatic relief in some of these patients. Both the standard pull type and the needle knife sphincterotomy over a stent can be performed [83, 87]. A total of 64% pain relief on follow-up of 6.5 years was reported following EPS in patients with idiopathic CP [112]. Other authors observed high success rates of 98% and low complication rates of around 4% in retrospective analysis [113].

Risks of pancreatic sphincterotomy include early complications of pancreatitis (2%–12%), bleeding (0%–3%) and perforations (<1%), and late complications of sphincter stenosis (up to 10%) [83, 87, 114]. Placement of a nasopancreatic tube or pancreatic stent can reduce their incidence [87, 102]. In reference [87], a 3 Fr single-pigtail plastic stent, 4–6 cm in length had been used to prevent postprocedure pancreatitis. The small-diameter single-pigtail stent generally passes into the gastrointestinal tract within 7–14 days without the need for a second endoscopic procedure for stent retrieval. A randomized study showed a higher incidence of pancreatitis in high-risk patients following pull-type sphincterotomy as compared to the

needle knife technique [115]. Restenosis is reported in around 14% of patients on long-term follow-up [116]. It is less common after the pull-type EPS with longer incision than the needle knife technique [117]. On the other hand, the use of EPS as a single therapeutic manipulation in patients with mild CP has not been studied well [86-89]. Therefore, endoscopic therapy is recommended as the first-line therapy for painful uncomplicated CP only in patients with moderate or marked changes at pancreatography according to the Cambridge classification.

2.2. Pancreatic duct stones

Nonsurgical clearance of stones obstruction of MPD can be achieved by ESWL or endoscopy alone, and by both of these techniques [83, 86-90]. In most patients, EPS with or without a biliary sphincterotomy via the major or minor papilla is performed to facilitate removal of pancreatic stones. The MPD stones are often impacted and difficult to extract, but up to 50% of MPD stones can be removed effectively by standard techniques, including endoscopic sphincterotomy or stone retrieval with a balloon, basket, and/or forceps alone [90, 101, 118-120]**.** Endoscopic stent placement, mechanical lithotripsy, intracorporeal lithotripsy with a pulse-dye laser, or electrohydraulic lithotripsy, are other possibilities [90, 121-125]. Adding ESWL increases clearance rates to 60%–90% [90]. The best candidates for endoscopic removal are MPD stones of the head or body with upstream MPD dilation [87, 90]. These devices are used to sweep or capture pancreatic duct stones to deliver stones, sludge, and debris out of the duct system and into the small-bowel lumen. Extraction balloons are very safe to use during ERCP [126]. Smaller pancreatic stone baskets are more effective if the duct lumen is less than 5 mm. In a case series, it was reported that endoscopic balloon dilation (12–15 mm) of the pancreatic orifice after sphincterotomy is a safe technique that facilitates the removal of large radiolucent stones from the MPD [127]. Further studies are needed before routine use of such large balloons can be recommended. On the other hand, in [86], the low success rate in a retrospective series of endoscopic stone extraction using Dormia baskets is discussed. In addition, mechanical lithotripsies are associated with relatively high morbidity rates in retrospective multicenter series [125].

ESWL has been usually used to facilitate the removal of PD stones during therapeutic endoscopy, especially in larger stones more than 5 mm in size [83, 86-90]. ESWL is now accepted as the standard of care in treatment of MPD stones. ESWL is highly effective at fragmenting radiopaque and radiolucent stones with high level of spontaneous elimination of stone fragments and pain relief [83, 86, 88, 90, 101]. In ESGE Guideline [86], successful stone fragmentation following ESWL has been defined as stones broken into fragments ≤2 or 3 mm, or by the demonstration of a decreased stone density at X-ray, an increased stone surface, and a heterogeneity of the stone which may fill the MPD and adjacent side branches. The ESGE Guideline group prefers the latter definition [86]. Performance of ESWL prior to endoscopy was associated with the success of MPD stone clearance in a retrospective study [111]. A meta-analysis of 17 studies with a total of 491 patients revealed a clearance rate between 37% and 100% and decreasing pain [128]. A review of 11 studies with over 1100 patients showed successful stone fragmentation in 89% [129]. Other authors reported complete clearance in 76% of 1000 patients and partial clearance in another 17% patients following ESWL and endother-

apy for large stones [101]. According to their opinion, patients with pain and large MPD stones in the head or body can be treated by ESWL. Patients with isolated calculi in the tail; multiple MPD strictures; extensive calculi in head, body, and tail; associated head mass; pseudocysts; and pregnancy are excluded from ESWL [83]. In [86], it has been discussed that in the majority of series, stones targeted by ESWL were mostly obstructive radiopaque MPD stones with a minimal diameter in the range of 2–5 mm. It has been also confirmed that factors significantly associated with success of MPD stone clearance after ESWL included the presence of a single stone, and confinement of calculi to the head of the pancreas.

A few studies have advocated the use of ESWL alone followed by spontaneous expulsion of fragments [83]. Patients frequently require several ESWL sessions to achieve stone clearance from the duct [130]. The results of uncontrolled series, including 350 patients followed-up for 44 months, showed spontaneous MPD stone clearance in 70%–88% of patients and long-term pain relief in 78% of patients [98, 131], whereas other investigators have had less impressive results [109, 132]. It has been discussed that complete removal rates differ among institutions [90]. These differences may be due to the type of lithotriptor used, the power setting, the number of shocks delivered, the number of treatment sessions, and differences regarding the definition of complete removal of pancreatic stones among institutions. A randomized controlled trial of 55 patients compared the performance of ESWL plus ERCP or ESWL alone [111]. The only significant differences between the groups were the longer hospital stay and a higher treatment cost in the ESWL plus ERCP group. ESWL is a relatively safe technique. The minor complications from ESWL include skin or duodenal lesions, exacerbation of pancreatitis, mild abdominal discomfort, and asymptomatic hyperamylasemia. Acute pancreatitis attributed to ESWL has been reported in 6.0%–12.5% of patients after ESWL "alone" for treating calcified CP [97, 98, 111, 131]. Serious complications after ESWL have been reported in less than 1% of patients [133]. The reported morbidity and mortality rates are 5.8% and 0.05%, respectively [97, 98, 101, 124]. Contraindications to ESWL include coagulation disorders, pregnancy, and presence in the shockwave path of bone, calcified aneurysms, or lung tissue [86]. Implanted cardiac pacemakers are not universally contraindicated to ESWL [134].

Finally, ESWL combined or not with ERCP is recommended as the first-line therapy for painful uncomplicated CP. The last ESGE Guideline [86] recommended: "For treating patients with radiopaque stones ≥ 5mm obstructing the MPD, ESWL as a first step, immediately followed by endoscopic extraction of stone fragments. In centers with considerable experience with ESWL, ESWL alone should be preferred over ESWL systematically combined with ERCP (Recommendation grade B). Endoscopic attempts to extract radiopaque MPD stones without prior stone fragmentation should be considered only for stones <5mm, preferably low in number, and located in the head or body of the pancreas. Intraductal lithotripsy should be attempted only after failure of ESWL (*Recommendation grade D*)". Intraductal laser or electrohydraulic lithotripsy are second-line interventions after failed ESWL, with success rates for stone fragmentation of 47%–83% [135, 136]. Stone dissolution therapy may have a role only in patients in whom all other methods have failed and who are not surgical candidates [86].

Several studies reported that pain relapse occurs more frequently with incomplete stone removal [97, 137, 138]. In contrast, other series reported no difference in pain relapse rates

between complete and incomplete removal groups [132, 139]. In one study, all patients with relapse had intraductal pancreatic stones, suggesting that the main cause of pain relapse is recurrent (or remnant) pancreatic stones [97]. Failure to achieve pain relief despite adequate clearance of the pancreatic duct stones indicates other mechanisms of pain in patients with CP.

2.3. Pancreatic ductal strictures

Endoscopic therapy is indicated for single strictures in the head while isolated strictures in the tail or multiple strictures are not amenable to endotherapy [85, 87]. Prior to MPD stenting, EPS of the major or minor papilla has been performed [83, 86, 87, 140]. Stricture dilation with Teflon bougies, Sohendra stent retriever, or a balloon dilator is also performed prior to stenting in most cases. High-grade strictures require dilation prior to insertion of the endoprosthesis [86, 87]. Because chronic pancreatitis-related MPD strictures may be very tight and resilient, dilation alone of the pancreatic duct stenosis is not a useful treatment [87, 88]. Large bore plastic stents should be deployed as they have longer patency [140]. Stents measuring 8.5 Fr or 10 Fr in diameter are used in most studies. A retrospective study of 163 patients showed that thinner MPD stents (≤8.5 Fr) are associated with 3 times more frequent hospitalizations for abdominal pain than 10-Fr stents [141]. In addition, stents should be kept in place for a long time (1–2 years) and require replacement in cases of obstruction and recurring symptoms [142]. MPD stenting for a short duration (6 months) has been shown to be poorly effective. The recurrence rate of pain after the stent removal was 30%–48%; as such pain often improves when a new stent is placed [86, 95, 105, 106]. In [140], a protocol was followed where a single stent was placed across a stricture and exchanged every 6 months or when the patient was symptomatic. Stents were placed for 24 months. Patients were restented if symptoms recurred. Surgery was considered if patients responded to stent placement but needed frequent or repeated stenting. Placement of a single pancreatic plastic stent achieves MPD stricture resolution in nearly 60% of cases [86]. Cumulative data from several trials showed that pancreatic stenting is technically successful in 85%–98% of cases, revealed pain relief in 65%–95%. Sustained pain relief was observed between 32% and 90% of patients on follow-up of 14–69 months [85, 105-108, 143, 144]. Recurrence of strictures was reported in 38% of patients after 2-year follow-up [96]. Restenting was reported in 22%–30% of patients, and 4%–26% of patients had pancreatic surgery. A pancreas divisum anatomy might require longer/multiple stenting because it is associated with more frequent relapse of MPD stricture and of pain after stent removal compared with MPD stenting in patients without pancreas divisum. Simultaneous placement of multiple pancreatic stents was reported to be of additional benefit. Other authors reported that after removal of a single stent, the stricture was dilated and multiple (mean of 3) plastic stents 8.5–11.5 Fr diameter were placed [145]. The stents were removed 12 months later. Stricture resolution was observed in 95% and pain relief in 84% on a 38-month follow-up.

Complications related to pancreatic stenting are reported between 6% and 39% [80, 105, 106, 143, 144]. They are usually mild and managed conservatively [83]. Mild pancreatitis is the most frequent complication of MPD stenting. Occlusion of stents requires stent exchange. Usually stent exchange was performed every 3 months or when symptoms developed [105-107]. The aim of an "on-demand" stent exchange schedule is to reduce the number of ERCP sessions

http://dx.doi.org/10.5772/60589

because occlusion usually occurs within 2–3 months, but symptoms of CP recur between 6 and 12 months [104]. Using of "on-demand" stent exchange schedule associate rare occurrence of pancreatic abscesses and sepsis [80, 95], and failure to decrease the number of ERCP sessions [95, 105]. MPD stent migration was present in 10% of patients [121]. Distal migration and impaction on the duodenal wall can cause perforation while proximal migration into the pancreas is a technical challenge for the endoscopist [83]. Proximal or distal stent migrations as well as pancreatic abscesses requiring surgery have rarely been reported. Because of elevated risk for pancreatic cancer, tissue samples are needed before endotherapy [146]. In addition, MPD stents may produce ductal changes, including strictures or focal areas of chronic pancreatitis [147, 148]. However, these changes may improve with time.

The ESGE recommended "treating dominant MPD stricture by inserting a single 10-Fr plastic stent, with stent exchange planned within 1 year even in asymptomatic patients to prevent complications related to long-standing pancreatic stent occlusion (Recommendation grade C)" [86]. Simultaneous placement of multiple, side-by-side, pancreatic stents could be applied more extensively, particularly in patients with MPD strictures persisting after 12 months of single plastic stenting. From this point of vew, the ESGE Guideline recommended that available options (e.g., endoscopic placement of multiple simultaneous MPD stents, surgery) be discussed by a multidisciplinary team (Recommendation grade D) [86]. In Spanish Pancreatic Club's guideline is pointed that pancreatic stenting is effective for treating short-term pain in patients with pancreatic duct stenosis, but it requires multiple ERCPs during follow-up, as well as pancreatic stents must be maintained for at least 12 months [88].

The search for an ideal pancreatic stent continues and a new "wing stent" to prevent clogging as well as an "S" shaped stent to prevent migration are undergoing evaluation [107, 149]. In one study in 20 patients, inserted self-expandable, uncovered Wallstents and partially or totally covered Wallstents in 18 patients with CP associated with dominant stricture of the MPD [150]. The results using uncovered Wall stents were unsatisfactory because of frequent stent dysfunction caused by tissue ingrowth (65%) through the wire mesh. In cases using partially or totally covered stents, epithelial hyperplasia and stent migration were the major late complications. The authors concluded that self-expandable stents provided disappointing results. The use of covered self-expandable metal stents (CSEMS) for pancreatic strictures now is also under evaluation. Preliminary data show that CSEMS is safe. They also allow pain relief and resolution of MPD strictures in a majority of patients, but no follow-up longer than 1 year is available [86]. The initially used CSEMS had the disadvantage of stent migration. A new "bumpy stent" has antimigratory properties and its contours adapted to the MPD. The stents were extracted at 3 months and were effective in resolving the MPD strictures [151, 152]. However, they were associated with the formation of de novo focal MPD strictures (16% of 32 patients). Further trials are needed to evaluate their long-term efficacy and safety. According to the ESGE Guideline [86], uncovered SEMS should not be inserted in MPD strictures (Recommendation grade D); temporary placement of fully CSEMS holds promise but it should be performed only in the setting of trials with approval of the institutional review board (Recommendation grade C).

Endosonography-guided access and drainage (ESGAD) of the MPD in CP-related MPD stricture includes puncturing the MPD through the gastric or duodenal wall, obtaining a pancreatogram and advancing a guide wire into the MPD to proceed with transpapillary (rendezvous technique) or transmural drainage [129]. The duodenal route is preferred [85]. ESGAD was effective in obtaining MPD drainage and pain relief (between 50% and100%) in selected patients with painful obstructive CP with mild morbidity. Some data have shown pain relief dropped with time from 69% to 20% after 450 days [153, 154]. In addition, some patients had a diagnosis of cancer within a year of the procedure. Reported complications related to ESGAD of the MPD are between 0% and 55% [91-94]. Most of them include relatively mild postprocedure pain, but severe pancreatitis, perforation, bleeding, and hematoma have been also observed [153-158]. No procedure-related mortality has been reported. Migration and occlusion of stents occur in 20%–55% of patients, necessitating endoscopic reintervention. No mortality was observed. On the basis of these data, ESGE [86] recommended: "ESGAD of the MPD is indicated in carefully selected patients; patients considered for ESGAD should be referred to tertiary centers with appropriate equipment and expertise (Evidence level 3, Recommendation grade D)." Potential indications for ESGAD of the MPD include patients with a symptomatic MPD obstruction and failed conventional transpapillary MPD drainage. In a randomized trial comparing endoscopic transampullary drainage of the MPD and operative pancreaticojejunostomy, complete or partial pain relief was achieved in 32% of the patients receiving endoscopic drainage and in 75% of the patients receiving surgery [93]. The rate of complications, length of hospital stay, and changes in pancreatic function were similar between the two treatment groups, but patients receiving endoscopic treatment required more procedures than those in the surgery group (median of 8 vs 3). These data show that surgical drainage of the MPD was more effective than endoscopic treatment in patients with obstruction of the MPD related to CP.

2.4. Endoscopic Ultrasound-guided Celiac Plexus Block (EUS-guided CPB)

Patients who have failed to respond to intensive medical or endoscopic therapy and are not candidates suitable for surgery can be provided relief from pain by EUS-guided CPB. EUS-guided CPB is one option for life-quality improvement for patients with CP, and it can be used in patients with nondilated MPD [159]. A combination of corticosteroids (triamcinolone) and local anesthetic agents (bupivacaine) is injected into celiac plexus nerves and around the celiac plexus under EUS guidance [83, 86-88]. Celiac plexus neurolysis (CPN) involves injection of a neurolytic agent (absolute alcohol) into the celiac plexus to ablate or destroy the ganglia, thereby interrupting pain transmission [87]. There is no difference between central versus bilateral injections in EUS-guided CPB [160]. No benefit of adding triamcinolone to bupivacaine was observed [161]. Some investigators prefer to reserve alcohol to patients with cancer-related pain [162]. In [48] it has been discussed that alcohol-based EUS-guided CPN provided pain relief in 59%. Therefore, this procedure is effective in pain control due to CP, but with a relatively lower efficacy compared to oncologic disease. The development of techniques or new injected drugs seems to be needed.

Meta-analyses have reported that EUS-guided CPB provides pain relief in 51%–59% of patients with painful CP for a period of 3–6 months [87, 163, 164]. In a prospective series of 90 patients,

http://dx.doi.org/10.5772/60589

the proportion of patients with pain relief decreased from 55% immediately after EUS-guided CPB to 10% at 24 weeks [165]. However, the efficacy of this therapy remains unclear. Patients who are younger than 45 years or have previous pancreatic surgery are less likely to benefit. In two randomized controlled trials, EUS-guided CPB appears to be associated with better outcomes and low incidence of side effects, and patient preference, as well as is more cost-effective than CT-guided route [166, 167]. In addition, EUS-guided route is not associated with severe complications such as paraplegia and aortic pseudoaneurysms [168, 169]. EUS-guided nerve block can produce diarrhea, hypertension due to sympathetic blockade because of the relatively unopposed visceral parasympathetic activity [87, 164, 170].

The most common (30%–40% of patients) complications of EUS-guided CPB include transient diarrhea, abdominal pain/pain exacerbation, and hypotension. However, they are usually mild and self-limiting [48, 164, 171-172]. There are also infrequent reports of retroperitoneal bleeding, peripancreatic abscess, abdominal ischemia, permanent paralysis, and also death [48, 87]. It has been proposed that the risk of serious morbidity and mortality should be weighed against expected benefits particularly in patients with a long life-expectancy (i.e., patients with CP).

ESGE experts [86] recommended considering CPB only as a second-line treatment for pain in CP. EUS-guided CPB should be preferred over percutaneous CPB (Recommendation grade C).

2.5. Pancreatic Pseudocyst (PPC) in CP

Endoscopic treatment is indicated for symptomatic PPC (abdominal pain, gastric outlet obstruction, early satiety, weight loss, or jaundice) and infected or enlarging PPC [86, 88, 89, 173]. In most series, spontaneous resolution of PPC in CP is rare (0%–9%) [174-176]. Only a single series reported a higher (26%–39%) resolution rate after a long follow-up [87, 177].The duration and size of the pseudocyst do not accurately predict the probability of spontaneous resolution or the development of complications, but larger (>4 cm) and/or longer-lasting (>6 weeks) pseudocysts are generally the ones that require active treatment [178]. Therefore, prophylactic treatment can be performed in selected asymptomatic patients with aim to prevent complications as pancreatic-pleural fistula, cysts >5 mm lasting for over 6 weeks, compression of major vessels, intracystic hemorrhage, cyst wall >5 mm, and PPC with advanced MPD changes or pancreaticolithiasis (presence of large pancreatic stones in MPD) [178, 179].

Many factors such as the size of the pseudocyst, bulging on the gut lumen, ductal communication, coagulopathy/portal hypertension, tolerance to multiple procedures, and symptoms can affect PPS management. Endoscopic therapy of PPC includes insertion of a drain from the digestive lumen into the PPC, through the digestive wall (“transmural drainage”), through the papilla (“transpapillary drainage”), or a combination of these routes. Transpapillary PPC drainage is reserved for the case of direct communication between the PPC and the MPD, as well as for small cysts (<6 cm size) [83, 180-183]. Transmural drainage is used for PPC which bulge into the lumen of stomach or duodenum, and the distance between the gut wall and the pseudocyst is less than 1 cm, with no intervening major vascular structures [83, 86, 89].

Transduodenal drainage offers the best success when compared to transgastric drainage. This is because cystoduodenal fistulas tend to remain patent

longer than cystogastric fistulas. A chronic cyst with clear liquid contents can be drained with one or more stents. On the other hand, an infected cyst may be aided by irrigation with a nasocystic catheter [87]. Placement of pigtailed stents is better when compared to straight stents. Straight stents are associated with a higher rate of bleed (around 7%) as well as migration [184]. Stents should be left in place for a longer duration as their removal within 2 months is associated with a higher incidence of PPC recurrence [86, 185]. Pseudoaneurysm can complicate management of PPC because of the associated hemorrhage and consequent high mortality [186]. Prophylactic embolization of pseudoaneurysms prior to drainage of an adjacent PPC has been recommended [140]. EUS is ideal for drainage of nonbulging PPC and cysts up to 4 cm from the stomach or duodenal wall [187], as well as in patients with portal hypertension [87]. In the presence of collaterals, the site of drainage is better identified with EUS, thus making the procedure safer. Technical success of endoscopic treatment is usually defined as the ability to insert at least one stent from the PPC to the digestive lumen, or resolution of the fluid collection but not necessarily of symptoms [184, 188-189]. Short-term clinical success is usually defined as complete relief of the initial symptoms with a decrease in PPC diameter of at least 30%–50% at 1 month [190]. In a summary of clinical trials, stent placement was technically successful in 89% of the cases, with a success rate of 80%–95% at most centers, a recurrence rate of 10%–20%. Complications as bleeding, infection, perforation and leak were observed in 3%–34% and death in 0.3%-1% [86, 87, 184]. An infection is more likely with transpapillary drainage and a leak is more likely with transmural drainage. Routine antibiotic administration is needed for drainage of PPC [191]. These results are comparative or better than surgery. In addition, compared with surgery, endoscopic drainage of uncomplicated PPC provides similar long-term results at a lower cost, with shorter hospital stay, and better quality of life during the first 3 months following treatment. Procedure-related mortality is slightly lower with the endoscopic method [86]. Randomized controlled trials and large reviews of noncomparative historical series of endoscopic and surgical treatments have also showed that drainage via EUS is better or similar than surgery [189, 192-194]. In [189], transmural and transpapillary drainage in 116 patients with PPC was compared. Successful resolution of symptoms and collection occurred in 88% of the cases. No significant differences were observed related to drainage technique or drainage site. In three nonrandomized studies, transpapillary drainage was used for smaller PPCs than transmural drainage [182, 190, 195]. Transpapillary drainage was associated with lower morbidity (1.8% vs 15.4%) and similar long-term success (94.6% vs 89.7%) than transmural drainage.

Technical success was higher with EUS-transmural PPC drainage compared to conventional guidance in randomized controlled trials [188, 193]. All patients with failed conventional drainage had a successful EUS-guided drainage. The complication rate was similar when PPCs are drained with or without EUS guidance [188, 190]. Cystoduodenostomy is associated with more long-term success than cystogastrostomy (83.1% vs 64.0%, respectively) but identical morbidity (10%) [196]. PPC drainage with a single stent and a stenting duration ≤6 weeks were independently associated with failure of endoscopic treatment [184].

On the base of these data, the ESGE Guideline [86] recommended endoscopic therapy as the first-line therapy for uncomplicated chronic PPC for which treatment is indicated and that are within endoscopic reach (Recommendation grade A). "If transmural pseudocyst drainage is indicated in the absence of luminal bulging, it should be performed under EUS guidance (Recommendation grade A). For small collections communicating with the MPD in the head or body of the pancreas, use transpapillary drainage first. Cystoduodenostomy should be preferred over cystogastrostomy if both routes are deemed equally feasible. For transmural PPC drainage, insert at least two double-pigtail plastic stents (Recommendation grade D); these should not be retrieved before cyst resolution as determined by cross-sectional imaging and not before at least 2 months of stenting (Recommendation grade B). In the case of portal hypertension, transmural drainage should be performed under EUS guidance. If arterial pseudoaneurysms are detected in the vicinity of the PPC, arterial embolization should be considered prior to PPC drainage (Recommendation grade D), and antibiotic prophylaxis for endoscopic PPC drainage (Recommendation grade D)." In addition, the ESGE also recommended "besides transmural PPC drainage, attempting transpapillary bridging of MPD ruptures with a plastic stent. If the MPD rupture cannot be bridged, transmural stents should be left in place for as long as the disconnected pancreatic tail secretes pancreatic juice (typically, for years) (Recommendation grade D)."

2.6. CP-related biliary strictures

Generally accepted indications for treatment of CP-related biliary strictures are secondary biliary cirrhosis, biliary stones, progression of biliary stricture, cases with symptoms or asymptomatic elevation of serum alkaline phosphatase (>2 or 3 times the upper limit of normal values), and/or raised serum bilirubin for longer than 1 month [83, 86, 87, 197]. Biliary brushing as well as EUS-guided fine-needle aspiration is required to exclude the possibility of cancer [86, 87]. Endoscopic treatment for biliary strictures includes stricture dilation using single or multiple side-by-side plastic stents, as well as covered SEMS. Biliary strictures secondary to CP respond less well to stenting than all other benign biliary strictures because of less frequent resolve at the time of stent removal and are associated with more frequent relapses [198-200]. The presence of pancreatic head calcification is an important factor for failure of endoscopic therapy with single plastic biliary stent, but this factor may be less relevant if simultaneous multiple plastic stents are used [201, 202]. Some studies have shown that cholestasis can be effectively resolved in the short-term setting by plastic biliary stenting [203, 204]. Patients without restenosis showed improvement of hepatic fibrosis after long-term stenting [205]. Single plastic biliary stents are associated with poor resolution and higher relapse rate [83, 86]. Sustained benefit is seen in around 25% of patients on follow-up of 46 months [206]. Placement of simultaneous multiple plastic stents in CP-related biliary strictures is technically successful in over 95% of patients and offers the best results [83, 86]. Complete therapy requires approximately four ERCP procedures and stents exchanges performed every 3 months for minimum 1 year [83, 207]. On the other hand, in the latter series, stents were exchanged at ERCP only if they were clogged [86]. Single stents provided relief in 31% of 350 patients as compared to 62% in 50 patients who received multiple stents [83]. One nonrandomized study compared single and multiple biliary plastic stents in CP [202]. Clinically, success was reported

in 92% with multiple stents as compared to 24% with single stents. Plastic biliary stents placement in patients with alcoholic CP has been reported to be associated with high incidence of cholangitis, because of poor patient compliance with scheduled stent exchanges [208]. Treatment with uncovered SEMS is associated with a high long-term morbidity and not recommended. Placement of covered SEMS is an investigational option for CP-related biliary stenosis [86, 200, 209, 210]. Other authors reported that the use of SEMS for long-term stenting of benign biliary strictures due to CP was safe and that it provided successful and prolonged biliary drainage in a selected group of patients in whom surgical intervention was not possible or desirable [211]. A multicenter trial using fully covered SEMS in 127 patients of CP concluded that these prostheses are useful for treatment of biliary strictures in patients with CP [212]. In one systematic review of studies published from 2000 to 2012, the success rate and complications of covered SEMS versus multiple plastic stents in CP-related benign biliary strictures were compared [200]. A total of 12 SEMS (376 patients) and 13 plastic stent studies (570 patients) met the final inclusion criteria. A tendency to successful use of SEMS in strictures related to CP was shown. In SEMS use, the incidence of late adverse events was lower in CP-related strictures and the median number of ERCP was lower – 1.5 versus 3.9. Larger, prospective, randomized long-term studies are required to confirm these results [87].

There has been no head-to-head study comparing single or multiple plastic stents and metal stents in biliary strictures due to CP and surgery [83]. According to [88], surgery is the treatment of choice for symptomatic biliary stenosis. Stents should be reserved for patients with high surgical risk to temporarily stabilize or improve them for surgery or for patients who refuse surgical treatment. In such cases, the best results are obtained with the placement of multiple stents or metal-covered stents [202, 213].

The ESGE Guideline [86] recommends: "The choice between endoscopic and surgical treatment should rely on local expertise, local or systemic patient co-morbidities (e.g., portal cavernoma, cirrhosis) and expected patient compliance with repeat endoscopic procedures (Recommendation grade D). If endoscopic therapy is elected, the ESGE recommends temporary (1-year) placement of multiple, side-by-side, plastic biliary stents (Recommendation grade A). Because of the risk of fatal septic complications, a recall system should be set up to care for patients who do not present for scheduled stent exchanges. In cases of relapsing stricture after stent removal at 1 year, the options available, including surgical biliary drainage, should be evaluated by a multidisciplinary team (Recommendation grade D)".

Today, there are many effective new and standard endoscopic techniques for the treatment of CP, especially in patients with pain and dilated main pancreatic duct because of intraductal calculi and/or strictures, as well as symptomatic or complicated pseudocysts, and CP-related biliary strictures. Today, there is also better patient selection for specific techniques, leading to more effective treatment. Earlier endoscopic therapy is more effective, less invasive than surgery, and is associated with low morbidity and mortality. In addition, it can be repeated and does not interfere with subsequent surgical procedure. Endotherapy became the first-line treatment in selected patients with CP.

http://dx.doi.org/10.5772/60589

3. Endoscopic therapy in Pancreatic Cancer (PC)

In the last years, the role of endoscopy as a part of multidisciplinary management of PC has increased. Endoscopy (ERCP) and mainly endoscopic ultrasound (EUS) with EUS-FNA and/or core biopsy are one of the most sensitive methods for the diagnosis and staging of PC. Therapeutic endoscopy has an important role in the palliation of patients with inoperable PC, including endoprosthesis stent placement in cases with biliary or duodenal obstruction, and EUS-guided CPN to control the pain. Various EUS-guided procedures, as tumor ablation, injection of antitumor agents, fiducial placement, and brachytherapy have been used for therapy of selected cases with PC.

3.1. Endoscopic therapy in biliary/duodenal obstruction

PC is among the tumors with the worst prognosis, with very high mortality rate. Most cases with PC are diagnosed at an advanced stage when surgical resection is not possible. Patients with unresectable PC often develop biliary and/or duodenal obstruction during the course of their disease, which are related with various complications and negative impact on quality of life, and not rarely are a cause for discontinuation of chemotherapy [214, 215]. In the past, surgical bypasses (biliary–digestive and gastro–jejunal anastomoses) were used for palliative treatment of biliary or duodenal obstruction, but currently endoscopic stenting is the preferred method. In the literature, several studies have compared the endoscopic and surgical palliative treatment of jaundice or duodenal obstruction in patients with unresectable PC [216-223]. The summary results show an advantage to endoscopic treatment in terms of quality of life, duration of hospitalization, and cost. The results of meta-analysis by the Cochrane Collaboration showed that rate of technical success and short-term efficacy in comparison of palliative endoscopic biliary drainage and surgical drainage for obstructing pancreatic carcinoma were similar, but the morbidity and duration of hospitalization are higher for surgical bypass [217, 218]. It was reported by various authors that endoscopic treatment of duodenal stenosis compared to bypass surgery was related with fewer complications, shorter hospitalization, and lower cost [219-223].

Endoscopic treatment of biliary obstruction includes placement of biliary stent (plastic or SEMS) during ERCP. The procedure is often associated with sphincterotomy, which facilitates the insertion of the prosthesis or its eventual replacement [214]. The results of randomized clinical studies showed that the success rate of endoscopic biliary stenting is over 90% of unselected patients with PC, with a morbidity of 5% [217]. The type of prosthesis does not influence the success rate of stent insertion and short-term efficacy, defined as regression of jaundice, pruritus, and a decrease of serum bilirubin more than 20%. If cholangitis develops or if bilirubin fails to fall by 20% within the first week after stent insertion, the patency and position of the stent must be verified [214]. Placement of SEMS is the cost-saving strategy, as plastic stents are associated with higher risk of recurrent biliary obstruction and consequently with need of additional procedures and hospitalizations [217, 224-229]. On the basis of cost-effectiveness analyses, the insertion of a metal prosthesis (more expensive but with a longer duration of patency) has been recommended if the patient's life expectancy is longer than 4

months [230]. Insertion of SEMS was advised in cases with biliary SEMS occlusion, as it provided longer patency and survival and decreased the number of subsequent procedures by 50% (compared to plastic stents) [229]. Technical failure during ERCP is encountered in up to 10% of cases due to various factors (duodenal obstruction, anatomical variations, periampullary diverticulum, tightness of the stricture) [214, 215]. In these cases, percutaneous transhepatic biliary drainage (PTBD), EUS-guided biliary drainage (BD), and surgical drainage are possible alternatives. The technical success rate for PTBD placement is 90% if the intrahepatic system is dilated and 70% in a nondilated system. The morbidity is 7% and the mortality is 5%, and it is contraindicated in the presence of ascites and coagulopathy. The results of recent systematic review on studies of EUS-guided biliary drainage (1127 published cases) showed that the mean technical and clinical success rates were of 91% and 88%, respectively, with the mean overall complication rate of 26% and mortality 0.4% [48].The authors of one recent study of 25 patients with unresectable malignant biliary obstruction and a previous failed ERCP attempt reported 100% technical and clinical success after the use of one of both procedures – percutaneous transhepatic biliary drainage or EUS-guided BD – with no difference in incidence of adverse events [231]. It is summarized that EUS-guided BD appears to be a valid alternative to percutaneous BD, showing similar efficacy and safety [48]. EUS-guided BD can be performed by one of the following approaches: direct transluminal stenting via transgastric or transduodenal route, by rendezvous technique passing a guidewire through an intrahepatic or extrahepatic access to the papilla, and by antegrade stent placement. EUS-guided transhepatic access was associated with a higher incidence of complications compared to the extrahepatic route (30.5% vs 9.3%), although the both access routes showed similar success rates [232]. In comparison the outcomes of rendezvous technique and transluminal approach of EUS-guided BD it was found that the effectiveness and safety of the both techniques were the same [233].

Endoscopic treatment of duodenal stenosis, due to invasion of PC, includes placement of an SEMS through the duodenoscope (Figure 4) [214, 215, 234]. The reported success rate is 92%–100% and rapid alimentary recovery (usually within 24 h) occurs in 75%–93% of cases [217]. Early complications have been reported in 2%–12% of cases, including perforation, gastrointestinal hemorrhage, aspiration pneumonia, jaundice or cholangitis, acute pancreatitis. The main cause of failure is downstream obstruction by unrecognized carcinomatosis, insufficient length to bridge the stenosis, prosthetic obstruction (food impaction or tumor ingrowth), or migration of the prosthesis [214]. Duodenal stenting should be reserved for symptomatic stricture since the introduction of prostheses into noncritical strictures is associated with a greater risk of stent migration. In appearance of prosthetic obstruction, a repeat procedure may be necessary (approximately 15% of cases) with insertion of a new prosthesis through the original stent [223]. If endoscopic insertion of a duodenal stent is impossible, a percutaneous transgastric approach is alternative. In cases with associated jaundice, endoscopic management begins with the placement of a metal biliary stent and followed by placement of the duodenal stent. The biliary drainage must always precede the duodenal stent placement [235]. If a biliary stent has previously been placed, its patency should be confirmed before placing the duodenal stent and replaced if necessary. If jaundice develops after duodenal stenting, the alternatives approaches to the biliary tract as PTBD or EUS-guided BD could be used.

http://dx.doi.org/10.5772/60589

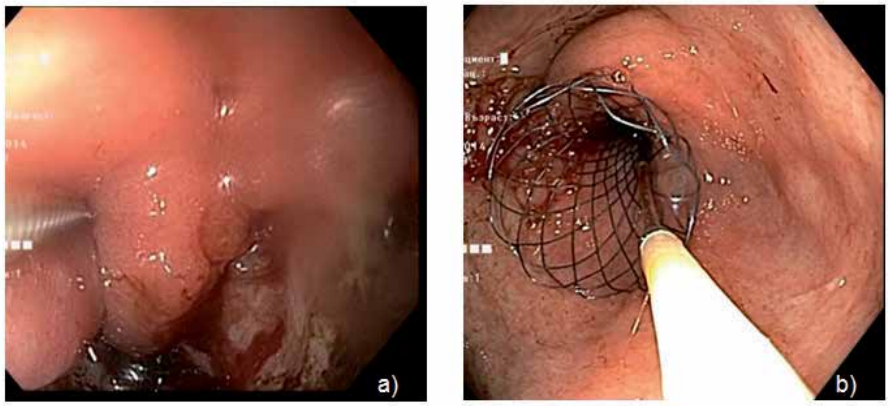

Figure 4. Palliative endoscopic management of PC. a) A view of pyloric infiltration and duodenal obstruction in a case with PC. b) Insertion of SEMS.

3.2. Endoscopic therapy for pain relief

Pain is reported in the majority of patients with advanced pancreatic cancer (90%) and its palliation is often difficult [215]. About 15% of patients with inoperable PC, having dilated main pancreatic beyond the stricture and an "obstructive" pain related to meals, may potentially benefit from endoscopic pancreatic stenting [236]. It was reported that pancreatic stenting may be obtained in more than 80% of these selected patients, with low morbidity (less than 10%), and no procedure-related mortality; approximately 60% of patients treated because of "obstructive" pain become symptom-free, and another 20%–25% significantly reduce the amount of analgesic drugs. In the last years, a number of studies have shown that effective pain control can be achieved in 70%–90% of advanced PC with EUS-guided celiac plexus neurolysis (CPN) [48, 163, 163, 237-244]. Significant reduction of pain scores 12 weeks after CPN was observed in 30 patients with advanced intraabdominal malignancy, while 91% of these patients required same or less pain medication and 88% of patients had persistent improvement in their pain score [237]. In one retrospective analysis of response to CPN in a cohort 64 patients with PC, it was found that visualization of the celiac ganglia was the best predictor of response: patients with visible ganglia were >15 times more likely to respond [242]. The results of two meta-analyses (including 8 studies/283 patients and 5 studies/119 patients) showed that the pooled proportion of patients that experienced pain relief was 80.1% and 72.5% after alcohol-based EUS-CPN [163, 164]. In a recent randomized clinical trial of 96 patients with advanced pancreatic cancer who were randomly assigned to early EUS-guided CPN or to conventional pain management, greater pain relief and a tendency toward lower morphine consumption was observed in the EUS-guided CPN group at 3 months [240]. It was also demonstrated that EUS-guided CPN significantly reduced pain, at 4 and 8 weeks, and opioid consumption in comparison with opiods intake alone [241]. It was summarized that EUS-guided CPN is superior to analgesic therapy in reducing pain in patients with PC. The results of one study, including 50 patients with PC, showed that there were no differences

regarding the onset or duration of pain relief in comparison between central and bilateral alcohol injections in EUS-guided CPN [243]. Some authors found that EUS-direct celiac ganglia neurolysis is superior to conventional EUS-guided CPN in inducing pain relief, with a higher treatment response rate (73.5% vs 45.5%) and complete response rate (50.0% vs 18.2%) [244].

3.3. EUS-guided antitumor therapies

For a short time, the use of various EUS-guided antitumor treatments has been reported in patients with locally advanced PC. The efficacy of EUS-guided ethanol injection alone or in combination with paclitaxel in pancreatic cystic lesions was reported in several studies [245-250]. A pilot study reported the efficacy of EUS-guided ethanol lavage in 25 patients with different cystic pancreatic lesions, with no side effects or complications during follow-up [245]. It was found that EUS-guided ethanol lavage led to a greater reduction in cyst size compared to simple saline injection (43% vs 11%) and resulted in complete cyst ablation in 33% of cases (12 out of 36) [246]. Follow-up by CT scan at 2 years of patients who had obtained complete cyst ablation after treatment showed persistent resolution of pancreatic cystic lesions in 75% of cases [247]. Addition of paclitaxel to ethanol injection showed a greater treatment rate of pancreatic cystic lesions compared to ethanol alone, with observed complete resolution in 62% of patients after 1-year follow-up [248, 249]. In addition, the use of EUS-guided ethanol injection was reported also in a small number of patients with pancreatic insulinoma [251-253]. In 3/5 patients with insulinoma, EUS-guided ethanol injection was related with symptoms resolution and no complications [251]. The main potential problem of EUS-guided ethanol ablation is the risk of acute pancreatitis due to diffusion of alcohol outside the lesion into the main pancreatic duct and/or the pancreatic parenchyma [254].

EUS-fine needle injection (FNI) is a simple technique to deliver chemotherapeutic agents into tumoral tissue for the treatment of locally advanced pancreatic cancer [48]. The technical success rate of all the studies about EUS-FNI reached 100%, paralleling the ability of performing EUS-FNA for cytological diagnosis. The clinical outcome varied greatly according to the different chemical or biological agents being tested [255]. In the literature, there are few small-size studies reporting the safety and feasibility of direct injection of different agents in patients with PC. One study tested the safety and efficacy of FNI of allogeneic mixed lymphocyte culture in 8 patients with locally advanced PC [256]. The authors reported that the procedure was safe and two partial responses and one minor response were reported (median survival 13.2 months). In other study (n=21 patients with PC), assessing the effect of EUS-FNI of adenovirus ONYX-015 in combination with systemic gemcitabine reported 2 patients with partial regression and 2 with minor response, but 4 serious adverse events (2 sepsis and 2 duodenal perforations) [257]. In the pilot study (n=7) with EUS-FNI of immature dendritic cells (inductors of primary T-cell response against tumor antigens), there were 1 complete and 3 partial responses reported and no adverse events [258]. In a multicenter study (n=50), the effect of EUS-FNI of TNFerade (a replication-deficient adenovirus vector carrying the TNF-α gene) in combination with systemic fluorouracil was tested [259]. The investigators observed 1 complete response, 3 partial responses, and 12 patients with stable disease after treatment as additionally 7 patients became suitable for surgery. The safety, tolerability, and preliminary

http://dx.doi.org/10.5772/60589

efficacy of EUS-FNI of BC-819 (a DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences) in combination with chemoradiotherapy was tested in 6 patients with PC – 3 of them showed partial response and the other 2 patients who were downstaged were able to undergo surgical resection [260]. It is summarized that direct intratumoral of various agents through FNI in patients with advanced PC is technically easy, safe and can induce tumor downstaging in some cases. The role of this method for cancer therapy will increase with the refinement of echoendoscopes, delivery systems, and novel local antitumor agents [261-263].

EUS-guided radiofrequency ablation (RFA) could be also used as an alternative procedure of treatment in unoperable patients with PC, but its translation into clinical practice has been restricted because of limited data and procedure-related risks [264]. The performance and effectiveness of EUS-guided RFA has been tested in several experimental studies, using porcine models [264-266]. In one study, the safety and efficacy of EUS-guided cryothermal ablation was assessed in 22 patients with locally advanced PC [267]. Using a newly developed cryotherm probe, combining radiofrequency with cryogenic cooling, the authors reported that the procedure was technically successful in 16 patients (72%) with a reduction in tumor size in 6 of them and well-tolerability [56]. It is summarized that EUS-guided cryothermal ablation is feasible in a subset of patients with locally advanced pancreatic cancer, but their safety and clinical outcome need to be investigated in future studies.

Brachytherapy is a useful method for local control of various malignant tumors, including pancreas [48, 215]. The placement of radioactive seeds allows steady radiation, leading to localized ablation and avoiding the radiation of normal tissues surrounding the malignant lesion. The feasibility, safety, and efficacy of EUS-guided implantation of iodine radioactive seeds in patients with locally advanced PC were assessed in a few studies [48, 268-270]. It was reported around 80% rate of positive response (decrease in tumor size) or stable disease, as well as improvements of pain scores and performance status scores. Adverse event rate was 0%–20%. Hematologic toxicity (neutropenia, thrombocytopenia, and anemia) was usually mild. Other complications reported less frequently were pancreatitis and pseudocyst formation. [268]. The studies demonstrated the technical feasibility of EUS-guided implantation of radioactive seeds in PC but larger studies evaluating the clinical outcome in a multimodality approach, combining chemotherapy and/or radiotherapy are needed [215, 238].

EUS-guided fiducial placement to facilitate stereotactic radiotherapy was assessed in several studies and was shown that it is a safe and precise, less invasive procedure [48, 215, 238, 271]. The placement of radiopaque fiducials inside or near the tumor allows performance of targeted radiotherapy with higher doses while sparing adjacent healthy tissue. Two studies of EUS-guided fiducial placement in a total of 101 patients with locally advanced PC reported high technical and clinical success rates (88%–90%) [272, 273]. Overall complication rate was low with only few minor adverse events (1 patient – a minor bleeding from the site of EUS needle entrance and 2 – mild pancreatitis). Migration of the gold fiducials was reported in 7% of cases. Another study observed no differences in visibility, migration, number of fiducial placement, technical difficulty, as well as in complication rate comparing two different types of fiducials (traditional vs coiled) [274].

In conclusion, today endoscopic therapy with or without EUS is an approved management option in selected patients with acute or chronc pancreatitis, or pancreatic cancer, showing the advantages of minimally invasive method of treatment. It should be performed in specialized centers with availaible multidisciplinary team.

Author details

Borislav Vladimirov[1*], Plamen Getzov[2] and Radina Ivanova[3]

*Address all correspondence to: borislavvladimirov@yahoo.com

1 Clinic of Gastroenterology, University Hospital Tz. Joanna, Medical University of Sofia, Bulgaria

2 Department of imaging diagnostics, University Hospital Tz. Joanna, Medical University of Sofia, Bulgaria

3 Laboratory of clinical pathology, University Hospital of Endocrinology, Medical University of Sofia, Bulgaria

References

[1] Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108(9):1400–1415.

[2] Banks PA, Bollen TL, Dervenis C, Gooszen HG et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–111.

[3] Bahr MH, Davis BR, Vitale GC. Endoscopic management of acute pancreatitis. Surg Clin North Am 2013;93(3):563–584.

[4] Zerem E. Treatment of severe acute pancreatitis and its complications. World J Gastroenterol 2014;20(38):13879–13892.

[5] Werner J, Feuerbach S, Uhl W, Büchler MW. Management of acute pancreatitis: from surgery to interventional intensive care. Gut 2005;54:426–436.

[6] Büchler MW, Gloor B, Müller CA et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:619–626.

[7] Acosta JM, Rubio Galli OM, Rossi R et al. Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. J Am Coll Surg 1997;184:499–505.

[8] Kelly TR. Gallstone pancreatitis: the timing of surgery. Surgery 1980;88:345–350.

[9] Runkel NS, Buhr HJ, Herfarth C. Outcome after surgery for biliary pancreatitis. Eur J Surg 1996;162(4):307–313.

[10] Beltsis A, Kapetanos D. Early ERCP in acute biliary pancreatitis: 20 years of dispute. Ann Gastroenterol 2010;23(1):27–30.

[11] Kapetanos DJ. ERCP in acute biliary pancreatitis. World J Gastrointest Endosc 2010; (1):25–28.

[12] Fan ST, Lai EC, Mok FP et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228–232.

[13] Fölsch UR, Nitsche R, Lüdtke R et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997;336:237–242.

[14] Uhl W, Warshaw A, Imrie C et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2002;2:565–573.

[15] Neoptolemos JP, London NJ, James D et al. Controlled trail of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative management for acute pancreatitis due to gallstones. Lancet 1988;3:979–983.

[16] Neoptolemos JP, Carr-Locke DL, London N et al. ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis. Br J Surg 1988;75:954–960.

[17] Nowak A, Nowakowska-Dulawa E, Marek T et al. Final results of the prospective, randomzed, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis. Gastroenterology 1995;108:A380.

[18] Vladimirov B, Jaramov N, Grigorov N et al. Endoscopic versus conservative treatment of acute gallstone pancreatitis – early results and prevention of recurrence. Gut 2002;51(Suppl III):A246 (abstract).

[19] Oria A, Cimmino D, Ocampo C et al. Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. Ann Surg 2007;245:10–17.

[20] Ayub K, Imada R, Slavin J. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. Cochrane Database Syst Rev 2004;CD003630.

[21] Moretti A, Papi C, Aratari A et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. Dig Liver Dis 2008;40:379–385.

[22] Petrov MS, van Santvoort HC, Besselink MG et al. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis

without cholangitis: a meta-analysis of randomized trials. Ann Surg 2008;247:250–257.

[23] Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. Cochrane Database Syst Rev 2012;5:CD009779.

[24] Van Santvoort HC, Bakker OJ, Besselink MG et al. Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. Endoscopy 2011;43(1):8–13.

[25] Romagnuolo J, Bardou M, Rahme E et al. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. Ann Intern Med 2003;139:547–557.

[26] Garrow D, Miller S, Sinha D et al. Endoscopic ultrasound: a meta-analysis of test performance in suspected biliary obstruction. Clin Gastroenterol Hepatol 2007;5:616–623.

[27] Stabuc B, Drobne D, Ferkolj I et al. Acute biliary pancreatitis: detection of common bile duct stones with endoscopic ultrasound. Eur J Gastroenterol Hepatol 2008 ; 20:1171–1175.

[28] Ledro-Cano D. Suspected choledocholithiasis: endoscopic ultrasound or magnetic resonance cholangio-pancreatography? A systematic review. Eur J Gastroenterol Hepatol 2007;19:1007–1011.

[29] Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013 Jul–Aug; 13(4 Suppl 2):e1–e15.

[30] Nieuwenhuijs VB, Besselink MG, van Minnen LP, Gooszen HG. Surgical management of acute necrotizing pancreatitis: a 13-year experience and a systematic review. Scand J Gastroenterol Suppl 2003;(239):111–116.

[31] van Baal MC, van Santvoort HC, Bollen TL et al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. Br J Surg 2011;98:18–27.

[32] Zerem E, Imamović G, Sušić A, Haračić B. Step-up approach to infected necrotising pancreatitis: a 20-year experience of percutaneous drainage in a single centre. Dig Liver Dis 2011;43:478–483.

[33] Doctor N, Philip S, Gandhi V et al. Analysis of the delayed approach to the management of infected pancreatic necrosis. World J Gastroenterol 2011;17:366–371.

[34] Mier J, León EL, Castillo A et al. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg 1997;173:71–75.

[35] Besselink MG, Verwer TJ, Schoenmaeckers EJ et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg 2007;142:1194–1201.

[36] van Santvoort HC, Besselink MG, Bakker OJ et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Eng J Med 2010;362:1491–1502.

[37] Mukai S, Itoi T, Moriyasu F. Interventional endoscopy for the treatment of pancreatic pseudocyst and walled-off necrosis (with videos). J Hepatobiliary Pancreat Sci 2014;21(10):E75–E85.

[38] Freeman ML, Werner J, van Santvoort HC et al. International multidisciplinary panel of speakers and moderators. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas 2012;41(8):1176–1194.

[39] Voermans RP1, Besselink MG, Fockens P. Endoscopic management of walled-off pancreatic necrosis. J Hepatobiliary Pancreat Sci 2015;22(1):20–26.

[40] Baron TH, Kozarek RA. Endotherapy for organized pancreatic necrosis: perspectives after 20 years. Clin Gastroenterol Hepatol 2012;10(11):1202–1207.

[41] Bakker OJ, van Santvoort HC, van Brunschot S et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307(10):1053–1061.

[42] Haghshenasskashani A, Laurence JM, Kwan V et al. Endoscopic necrosectomy of pancreatic necrosis: a systematic review. Surg Endosc 2011;25(12):3724–3730.

[43] Puli SR, Graumlich JF, Pamulaparthy SR, Kalva N. Endoscopic transmural necrosectomy for walled-off pancreatic necrosis: a systematic review and meta-analysis. Can J Gastroenterol Hepatol 2014;28(1):50–53.

[44] van Brunschot S, Fockens P, Bakker OJ et al. Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review. Surg Endosc 2014;28(5):1425–1438.

[45] van Brunschot S, van Grinsven J, Voermans RP et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. BMC Gastroenterol 2013;13:161.

[46] Bang JY, Varadarajulu S. Endoscopic ultrasound-guided management of pancreatic pseudocysts and walled-off necrosis. Clin Endosc 2014;47(5):429–431.

[47] Baron TH, Thaggard WG, Morgan DE, Stanley RJ. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 1996;111:755–764.

[48] Fabbri C, Luigiano C, Lisotti A et al. Endoscopic ultrasound-guided treatments: are we getting evidence based – a systematic review. World J Gastroenterol 2014;20(26): 8424–8448.

[49] Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. Gastrointest Endosc 2011;74:74–80.

[50] Abdelhafez M, Elnegouly M, Hasab Allah MS et al. Transluminal retroperitoneal endoscopic necrosectomy with the use of hydrogen peroxide and without external irrigation: a novel approach for the treatment of walled off pancreatic necrosis. Surg Endosc 2013;27:3911–3920.

[51] Siddiqui A, Easler J, Strongin A et al. Hydrogen peroxide-assisted endoscopic necrosectomy for walled-off pancreatic necrosis: a dual center pilot experience. Dig Dis Sci 2014;59:687–690.

[52] Itoi T, Binmoeller KF, Shah J et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). Gastrointest Endosc 2012;75:870–876.

[53] Yamamoto N, Isayama H, Kawakami H et al. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. Gastrointest Endosc 2013;77:809–814.

[54] Moon JH, Choi HJ, Kim DC et al. A newly designed fully covered metal stent for lumen apposition in EUS-guided drainage and access: a feasibility study (with videos). Gastrointest Endosc 2014;79:990–995.

[55] Papachristou GI, Takahashi N, Chahal P et al. Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis. Ann Surg 2007;245:943–951.

[56] Gardner TB, Coelho-Prabhu N, Gordon SR et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter US series. Gastrointest Endosc 2011;73:718–726.

[57] Klöppel G. Pseudocyst and other non-neoplastic cyst of the pancreas. Semin Diagn Pathol 2000;17:7–15.

[58] O'Malley VP, Cannon JP, Postier RG. Pancreatic pseudocysts: cause, therapy and results. Am J Surg 1985;150:680–2.

[59] Kozarek RA, Ball TJ, Patterson DJ et al. Endoscopic transpapillary therapy for disrupted pancreatic duct and peripancreatic fluid collections. Gastroenterology 1991;100:1362–1370.

[60] Varadarajulu S, Noone TC, Tutuian R et al. Predictors of outcome in pancreatic uct disruption managed by endoscopic transpapillary stent placement. Gastrointest Endosc 2005;61:568–575.

[61] Lawrence C, Howell DA, Stefan AM et al. Disconnected pancreatic tail syndrome: potential for endoscopic therapy and results of long-term follow-up. Gastrointest Endosc 2008;67:673–679.

[62] Telford JJ, Farrell JJ, Saltzman JR et al. Pancreatic stent placement for duct disruption. Gastrointest Endosc 2002;56:18–24.

[63] Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic pancreatitis, what should be done? World J Gastroenterol 2008;14:1007–1010.

[64] Kedia S, Dhingra R, Garg PK. Recurrent acute pancreatitis: an approach to diagnosis and management. Trop Gastroenterol 2013;34(3):123–135.

[65] Testoni PA. Acute recurrent pancreatitis: etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20(45):16891–16901.

[66] Lans JI, Geenen JE, Johanson JF, Hogan WJ. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. Gastrointest Endosc 1992;38:430–434.

[67] Liao Z, Gao R, Wang W et al. A systematic review on endoscopic detection rate, endotherapy, and surgery for pancreas divisum. Endoscopy 2009;41:439–444.

[68] Katsinelos P, Paroutoglou G, Chatzimavroudis G et al. Endoscopic sphincterotomy for acute relapsing pancreatitis associated with periampullary diverticula: a long-term follow-up. Acta Gastroenterol Belg 2007;70(2):195–8.

[69] Simpson WF, Adams DB, Metcalf JS et al. Nonfunctioning pancreatic neuroendocrine tumors presenting as pancreatitis: report of four cases. Pancreas 1988;3:223–231.

[70] Kohler H, Lankisch PG. Acute pancreatitis and hyperamylasaemia in pancreatic carcinoma. Pancreas 1987;2:117–119.

[71] Robertson JF, Imrie CW. Acute pancreatitis associated with carcinoma of the ampulla of Vater. Br J Surg 1987;74:395–397.

[72] Bank S, Indaram A. Causes of acute and recurrent pancreatitis. Clinical considerations and clues to diagnosis. Gastroenterol Clin North Am 1999;28:571–589.

[73] Attasaranya S, Abdel Aziz AM, Lehman GA. Endoscopic management of acute and chronic pancreatitis. Surg Clin North Am 2007;87:1379–402.

[74] Adler DG, Baron TH, Davila RE et al. ASGE guideline: the role of ERCP in disease of the biliary tract and the pancreas. Gastrointest Endosc 2005;62(1):1–8.

[75] Tarnasky PR, Palesch YY, Cunningham JT et al. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology 1998;115:1518–24.

[76] Hall TC, Dennison AR, Garcea G. The diagnosis and management of Sphincter of Oddi dysfunction: a systematic review. Langenbecks Arch Surg 2012;397:889–898.

[77] Heetun ZS, Zeb F, Cullen G et al. Biliary sphincter of Oddi dysfunction: response rates after ERCP and sphincterotomy in a 5-year ERCP series and proposal for new practical guidelines. Eur J Gastroenterol Hepatol 2011;23:327–333.

[78] Cote GA, Imperiale TF, Schmidt SE et al. Similar effects of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology 2012;143:1502–1509.

[79] Bradley EL. Long term results of pancreaticojejunostomy in patients with chronic pancreatitis. Am J Surg 1987;153:207–213.

[80] Cremer M, Devière J, Delhaye M et al. Stenting in severe chronic pancreatitis: results of medium term follow-up in seventy-six patients. Endoscopy 1991;23:171–176.

[81] Schnelldorfer T, Lewin DN, Adams DB. Operative management of chronic pancreatitis: longterm results in 372 patients. J Am Coll Surg 2007;204:1039–1045.

[82] Rösch T, Daniel S, Scholz M et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002;34:765–771.

[83] Tandan M, Reddy D N. Endotherapy in chronic pancreatitis. World J Gastroenterol 2013;19(37):6156–6164.

[84] Boustière C, Veitch A, Vanbiervliet G et al. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2011;43:445–461.

[85] Tringali A, Boskoski I, Costamagna G. The role of endoscopy in the therapy of chronic pancreatitis. Best Pract Res Clin Gastroenterol 2008;22:145–165.

[86] Dumonceau JM, Delhaye M, Tringali A et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2012;44(8):784–800.

[87] Yoo BM, Lehman GA. Update on endoscopic treatment of chronic pancreatitis. Korean J Intern Med 2009;24(3):169–179.

[88] de-Madaria E, Abad-González A, Aparicio JR et al. The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). Pancreatology 2013;13(1):18–28.

[89] Frulloni L, Falconi M, Gabbrielli A et al. Italian consensus guidelines for chronic pancreatitis. Dig Liver Dis 2010;42 Suppl 6:S381–S406.

[90] Choi EK, Lehman GA. Update on endoscopic management of main pancreatic duct stones in chronic calcific pancreatitis. Korean J Intern Med 2012;27(1):20–9.

[91] Vladimirov B, Mitova R, Grigorov N, Damjanov D, Korukov B, Parvanov P. Endoscopic versus conventional conservative therapy in chronic pancreatitis. Second Congress of Serbian gastroenterologists with international participation. 1–2.09.2011, Belgrade, Arch. Gastroenterohepatology, p.117.

[92] Díte P, Ruzicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003;35(7):553–558.

[93] Cahen DL, Gouma DJ, Nio Y et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356(7):676–684.

[94] Cahen DL, Gouma DJ, Laramée P et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology 2011;141(5):1690–1695.

[95] Binmoeller KF, Jue P, Seifert H et al. Endoscopic pancreatic stent drainage in chronic pancreatitis and a dominant stricture: long-term results. Endoscopy 1995;27:638–644.

[96] Delhaye M, Arvanitakis M, Verset G et al. Long-term clinical outcome after endoscopic pancreatic ductal drainage for patients with painful chronic pancreatitis. Clin Gastroenterol Hepatol 2004;2:1096–1106.

[97] Tadenuma H, Ishihara T, Yamaguchi T et al. Long-term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones. Clin Gastroenterol Hepatol 2005;3:1128–1135.

[98] Inui K, Tazuma S, Yamaguchi T et al. Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicenter survey. Pancreas 2005;30:26–30.

[99] Farnbacher MJ, Mühldorfer S,WehlerM et al. Interventional endoscopic therapy in chronic pancreatitis including temporary stenting: a definitive treatment? Scand J Gastroenterol 2006;41:111–117.

[100] Diener MK, Rahbari NN, Fischer L et al. Duodenum-preserving pancreatic head resection versus pancreatoduodenectomy for surgical treatment of chronic pancreatitis: a systematic review and meta-analysis. Ann Surg 2008;247:950–961.

[101] Tandan M, Reddy DN, Santosh D et al. Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi – a large single center experience. Indian J Gastroenterol 2010;29:143–148.

[102] Hookey LC, RioTinto R, Delhaye M et al. Risk factors for pancreatitis after pancreatic sphincterotomy: a review of 572 cases. Endoscopy 2006;38:670–676.

[103] Dumonceau J-M, Andriulli A, Deviere J et al. European Society of Gastrointestinal Endoscopy (ESGE) guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy 2010;42:503–515.

[104] Morgan DE, Smith JK, Hawkins K, Wilcox CM. Endoscopic stent therapy in advanced chronic pancreatitis: relationships between ductal changes, clinicalresponse, and stent patency. Am J Gastroenterol 2003;98:821–826.

[105] Eleftherladis N, Dinu F, Delhaye M et al. Long-term outcome after pancreatic stenting in severe chronic pancreatitis.Endoscopy 2005;37:223–230.

[106] Vitale GC, Cothron K, Vitale EA et al. Role of pancreatic duct stenting in the treatment of chronic pancreatitis. Surg Endosc 2004;18:1431–1434.

[107] Ishihara T, Yamaguchi T, Seza K et al. Efficacy of s-type stents for the treatment of the main pancreatic duct stricture in patients with chronic pancreatitis. Scand J Gastroenterol 2006;41:744–750.

[108] Weber A, Schneider J, Neu B et al. Endoscopic stent therapy for patients with chronic pancreatitis: results from a prospective follow-up study. Pancreas 2007;34:287–294.

[109] Brand B, Kahl M, Sidhu S et al. Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis. Am J Gastroenterol 2000;95:3428–3438.

[110] Dumonceau JM, Devière J, Le Moine O et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long term results. Gastrointest Endosc 1996;43:547–555.

[111] Dumonceau J-M, Costamagna G, Tringali A et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut 2007;56:545–552.

[112] Gabbrielli A, Mutignani M, Pandolfi M et al. Endotherapy of early onset idiopathic chronic pancreatitis: results with long-term follow-up. Gastrointest Endosc 2002;55:488–493.

[113] Ell C, Rabenstein T, Schneider HT, Ruppert T et al. Safety and efficacy of pancreatic sphincterotomy in chronic pancreatitis. Gastrointest Endosc 1998;48:244–249.

[114] Papachristou GI, Baron TH. Complication of therapeutic endoscopic retrograde cholangiopancreatography. Gut 2007;56:854–868.

[115] Varadarajulu S, Wilcox CM. Randomized trial comparing needle-knife and pull-sphincterotome techniques for pancreatic sphincterotomy in high-risk patients. Gastrointest Endosc 2006;64:716–722.

[116] Kozarek RA, Ball TJ, Patterson DJ et al. Endoscopic pancreatic duct sphincterotomy: indications, technique, and analysis of results. Gastrointest Endosc 1994;40:592–598.

[117] Siegel JH, Cohen SA. Pull or push pancreatic sphincterotomy for sphincter of Oddi dysfunction? A conundrum for experts only. Gastrointest Endosc 2006;64:723–725.

[118] Ong WC, Tandan M, Reddy V et al. Multiple main pancreatic duct stones in tropical pancreatitis: safe clearance with extracorporeal shockwave lithotripsy. J Gastroenterol Hepatol 2006;21:1514–1518.

[119] Lehman GA. Role of ERCP and other endoscopic modalities in chronic pancreatitis. Gastrointest Endosc 2002;56: S237–S240.

[120] Green JE, Vennes JA, Silvis SE. Resume of a seminar on endoscopic retrograde sphincterotomy (ERS). Gastrointest Endosc 1981;27:31–38.

[121] Adler DG, Lichtenstein D, Baron TH et al. The role of endoscopy in patients with chronic pancreatitis. Gastrointest Endosc 2006;63:933–937.

[122] Costamagna G, Gabbrielli A, Mutignani M et al. Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium-term results. Gastrointest Endosc 1997;46:231–236.

[123] Smits ME, Rauws EA, Tytgat GN, Huibregtse K. Endoscopic treatment of pancreatic stones in patients with chronic pancreatitis. Gastrointest Endosc 1996;43:556–560.

[124] Delhaye M, Vandermeeren A, Baize M, Cremer M. Extracorporeal shock-wave lithotripsy of pancreatic calculi. Gastroenterology 1992;102:610–620.

[125] Farnbacher MJ, Schoen C, Rabenstein T et al. Pancreatic duct stones in chronic pancreatitis: criteria for treatment intensity and success. Gastrointest Endosc 2002;56:501–506.

[126] Thomas M, Howell DA, Carr-Locke D et al. Mechanical lithotripsy of pancreatic and biliary stones: complications and available treatment options collected from expert centers. Am J Gastroenterol 2007;102:1896–1902.

[127] Maydeo A, Bhandari S, Bapat M. Endoscopic balloon sphincteroplasty for extraction of large radiolucent pancreatic duct stones (with videos). Gastrointest Endosc 2009;70:798–802.

[128] Guda NM, Partington S, Freeman ML. Extracorporeal shock wave lithotripsy in the management of chronic calcific pancreatitis: a meta-analysis. JOP 2005;6:6–12.

[129] Nguyen-Tang T, Dumonceau JM. Endoscopic treatment in chronic pancreatitis, timing, duration and type of intervention. Best Pract Res Clin Gastroenterol 2010;24:281–298.

[130] Maydeo A, Soehendra N, Reddy N, Bhandari S. Endotherapy for chronic pancreatitis with intracanalar stones. Endoscopy 2007;39:653–658.

[131] Ohara H, Hoshino M, Hayakawa T et al. Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones. Am J Gastroenterol 1996;91:1388–1394.

[132] Adamek HE, Jakobs R, Buttmann A et al. Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy. Gut 1999;45:402-405.

[133] Karakayali F, Sevmis S, Ayvaz I et al. Acute necrotizing pancreatitis as a rare complication of extracorporeal shock wave lithotripsy. Int J Urol 2006;13:613–615.

[134] Platonov MA, Gillis AM, Kavanagh KM. Pacemakers, implantable cardioverter/defibrillators, and extracorporeal shockwave lithotripsy: evidence-based guidelines for the modern era. J Endourol 2008;22:243–247.

[135] Hirai T, Goto H, Hirooka Y et al. Pilot study of pancreatoscopic lithotripsy using a 5-fr instrument: selected patients may benefit. Endoscopy 2004;36:212–216.

[136] Howell DA, Dy RM, Hanson BL et al. Endoscopic treatment of pancreatic duct stones using a 10F pancreatoscope and electrohydraulic lithotripsy. Gastrointest Endosc 1999;50:829–833.

[137] van der Hul R, Plaisier P, Jeekel J et al. Extracorporeal shock-wave lithotripsy of pancreatic duct stones: immediate and long-term results. Endoscopy 1994;26:573–578.

[138] Sauerbruch T, Holl J, Sackmann M, Paumgartner G. Extracorporeal lithotripsy of pancreatic stones in patients with chronic pancreatitis and pain: a prospective follow up study. Gut 1992;33:969–972.

[139] Schneider HT, May A, Benninger J et al. Piezoelectric shock wave lithotripsy of pancreatic duct stones. Am J Gastroenterol 1994;89:2042–2048.

[140] Delhaye M, Matos C, Devière J. Endoscopic technique for the management of pancreatitis and its complications. Best Pract Res Clin Gastroenterol 2004;18:155–181.

[141] Sauer BG, Gurka MJ, Ellen K et al. Effect of pancreatic duct stent diameter on hospitalization in chronic pancreatitis: does size matter? Pancreas 2009;38:728–731.

[142] Ponchon T, Bory RM, Hedelius F et al. Endoscopic stenting for pain relief in chronic pancreatitis: results of a standardized protocol. Gastrointest Endosc 1995;42:452–456.

[143] Smits ME, Badiga SM, Rauws EA et al. Long-term results of pancreatic stents in chronic pancreatitis. Gastrointest Endosc 1995;42:461–467.

[144] Boursier J, Quentin V, Le Tallec V et al. Endoscopic treatment of painful chronic pancreatitis: evaluation of a new flexible multiperforated plastic stent. Gastroenterol Clin Biol 2008;32:801–805.

[145] Costamagna G, Bulajic M, Tringali A et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006;38:254–259.

[146] Faigel DO, Eisen GM, Baron TH et al. Tissue sampling and analysis. Gastrointest Endosc 2003;57:811–816.

[147] Smith MT, Sherman S, Ikenberry SO et al. Alterations in pancreatic ductal morphology following polyethylene pancreatic stent therapy. Gastrointest Endosc 1996;44:268–275.

[148] Sherman S, Hawes RH, Savides TJ et al. Stent-induced pancreatic ductal and parenchymal changes: correlation of endoscopic ultrasound with ERCP. Gastrointest Endosc 1996;44:276–282.

[149] Raju GS, Gomez G, Xiao SY et al. Effect of a novel pancreatic stent design on short-term pancreatic injury in a canine model. Endoscopy 2006;38:260–265.

[150] Eisendrath P, Deviere J. Expandable metal stents for benign pancreatic duct obstruction. Gastrointest Endosc Clin N Am 1999;9:547–554.

[151] Park DH, Kim M-H, Moon S-H et al. Feasibility and safety of placement of a newly designed, fully covered self-expandable metal stent for refractory benign pancreatic ductal strictures: a pilot study (with video). Gastrointest Endosc 2008;68:1182–1189.

[152] Moon S-H, Kim M-H, Park DH et al. Modified fully covered self-expandable metal stents with antimigration features for benign pancreatic duct strictures in advanced chronic pancreatitis, with a focus on the safety profile and reducing migration. Gastrointest Endosc 2010;72:86–91.

[153] Tessier G, Bories E, Arvanitakis M et al. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. Gastrointest Endosc 2007;65:233–241.

[154] Kahaleh M, Hernandez AJ, Tokar J et al. EUS-guided pancreaticogastrostomy: analysis of its efficacy to drain inaccessible pancreatic ducts. Gastrointest Endosc 2007;65:224–230.

[155] Brauer BC, Chen YK, Fukami N, Shah RJ. Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video). Gastrointest Endosc 2009;70:471–479.

[156] François E, Kahaleh M, Giovannini M et al. EUS-guided pancreaticogastrostomy. Gastrointest Endosc 2002;56:128–133.

[157] Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. Gastrointest Endosc 2004;59:100–107.

[158] Will U, Fueldner F, Thieme A-K et al. Transgastric pancreatography and EUS-guided drainage of the pancreatic duct. J Hepatobiliary Pancreat Surg 2007;14:377–382.

[159] Michaels AJ, Draganov PV. Endoscopic ultrasonography guided celiac plexus neurolysis and celiac plexus block in the management of pain due to pancreatic cancer and chronic pancreatitis. World J Gastroenterol 2007;13:3575–3580.

[160] LeBlanc JK, DeWitt J, Johnson C et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. Gastrointest Endosc 2009;69:835–842.

[161] Stevens T, Costanzo A, Lopez R et al. Adding triamcinolone to endoscopic ultrasound-guided celiac plexus blockade does not reduce pain in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2012;10:186–191.

[162] Pateman J, Williams MP, Filshie J. Retroperitoneal fibrosis after multiple coeliac plexus blocks. Anaesthesia 1990;45:309–310.

[163] Puli SR, Reddy JBK, Bechtold ML et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic reviewDig Dis Sci 2009;54:2330–2337.

[164] Kaufman M, Singh G, Das S et al. Efficacy of endoscopic ultrasound guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol 2010;44:127–134.

[165] Gress F, Schmitt C, Sherman S et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. Am J Gastroenterol 2001;96:409–416.

[166] Gress F, Schmitt C, Sherman S et al. A prospective randomized comparisonof endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. Am J Gastroenterol 1999;94:900–905.

[167] Santosh D, Lakhtakia S, Gupta R et al. Clinical trial: a randomized trial comparing fluoroscopy guided percutaneous technique vs. endoscopic ultrasound guided technique of coeliac plexus block for treatment of pain in chronic pancreatitis. Aliment Pharmacol Ther 2009;29:979–984.

[168] Sett SS, Taylor DC. Aortic pseudoaneurysm secondary to celiac plexusblock. Ann Vasc Surg 1991;5:88–91.

[169] Davies DD. Incidence of major complications of neurolytic coeliac plexus block. J R Soc Med 1993;86:264–266.

[170] Sahai AV, Lemelin V, Lam E, Paquin SC. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. Am J Gastroenterol 2009;104:326–329.

[171] Levy MJ, Topazian MD, Wiersema MJ et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block. Am J Gastroenterol 2008;103:98–103.

[172] O'Toole TM, Schmulewitz N. Complication rates of EUS guided celiac plexus blockade and neurolysis: results of a large case series. Endoscopy 2009;41:593–597.

[173] Habashi S, Draganov PV. Pancreatic pseudocyst. World J Gastroenterol 2009;15:38–47.

[174] Andrén-Sandberg A, Dervenis C. Pancreatic pseudocysts in the 21st century. Part II: natural history. JOP 2004;5:64–70.

[175] Talar-Wojnarowska R, Wozniak B, Pazurek M, Malecka-Panas E. Outcome of pseudocysts complicating chronic pancreatitis. Hepatogastroenterology 2010;57:631–634.

[176] Cheruvu CV, Clarke MG, Prentice M, Eyre-Brook IA. Conservative treatment as an option in the management of pancreatic pseudocyst. Ann R Coll Surg Engl 2003;85:313–316.

[177] Gouyon B, Lévy P, Ruszniewski P et al. Predictive factors in the outcome of pseudocysts complicating alcoholic chronic pancreatitis. Gut 1997;41:821–825.

[178] Yeo CJ, Bastidas JA, Lynch-Nyhan A et al. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet 1990;170:411–417.

[179] Lerch MM, Stier A, Wahnschaffe U et al. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? Dtsch Arztebl Int 2009;106:614–621.

[180] Barkin JS, Hyder SA. Changing concepts in the management of pancreatic pseudocysts. Gastrointest Endosc 1989;35:62–64.

[181] Baron TH, Harewood GC, Morgan DE et al. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. Gastrointest Endosc 2002;6:7–17.

[182] Barthet M, Lamblin G, Gasmi M et al. Clinical usefulness of a treatment algorithm for pancreatic pseudocysts. Gastrointest Endosc 2008;67:245–252.

[183] Cremer M, Deviere J, Engelholm L. Endoscopic management of cysts and pseudocysts in chronic pancreatitis: long-term follow-up after 7 years of experience. Gastrointest Endosc 1989;35:1–9.

[184] Cahen D, Rauws E, Fockens P et al. Endoscopic drainage of pancreatic pseudocysts: long-term outcome and procedural factors associated with safe and successful treatment. Endoscopy 2005;37:977–983.

[185] Arvanitakis M, Delhaye M, Bali MA et al. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc 2007;65:609–619.

[186] Balachandra S, Siriwardena AK. Systematic appraisal of the management of the major vascular complications of pancreatitis. Am J Surg 2005;190:489–495.

[187] Sanchez Cortes E, Maalak A, Le Moine O et al. Endoscopic cystenterostomy of nonbulging pancreatic fluid collections. Gastrointest Endosc 2002;56:380–386.

[188] Park DH, Lee SS, Moon S-H et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy 2009;41:842–848.

[189] Hookey LC, Debroux S, Delhaye M et al. Endoscopic drainage of pancreatic fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. Gastrointest Endosc 2006;63:635–643.

[190] KahalehM, Shami VM, Conaway MR et al. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. Endoscopy 2006;38:355–359.

[191] Banerjee S, Shen B, Baron TH et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc 2008;67:791–798.

[192] Rosso E, Alexakis N, Ghaneh P et al. Pancreatic pseudocyst in chronic pancreatitis: endoscopic and surgical treatment. Dig Surg 2003;20:397–406.

[193] Varadarajulu S, Lopes TL, Wilcox CM et al. EUS versus surgical cyst-gastrostomy for management of pancreatic pseudocysts. Gastrointest Endosc 2008;68:649–655.

[194] Varadarajulu S, Bang JY, Sutton BS et al. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology 2013;145:583–590.

[195] Binmoeller KF, Seifert H, Walter A et al. Transpapillary and transmural drainage of pancreatic pseudocysts. Gastrointest Endosc 1995;42:219–224.

[196] Beckingham IJ, Krige JE, Bornman PC et al. Endoscopic management of pancreatic pseudocysts. Br J Surg 1997;84:1638–1645.

[197] Frey CF, Suzuki M, Isaji S. Treatment of chronic pancreatitis complicated by obstruction of the common bile duct or duodenum. World J Surg 1990;14:59–69.

[198] Kahaleh M, Behm B, Clarke BW et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video) Gastrointest Endosc 2008;67:446–454.

[199] Mahajan A, Ho H, Sauer B et al. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). Gastrointest Endosc 2009;70:303–309.

[200] Siiki A, Helminen M, Sand J, Laukkarinen J. Covered self-expanding metal stents may be preferable to plastic stents in the treatment of chronic pancreatitis-related biliary strictures: a systematic review comparing 2 methods of stent therapy in benign biliary strictures. J Clin Gastroenterol 2014;48(7):635–643.

[201] Kahl S, Zimmermann S, Genz I et al. Risk factors for failure of endoscopic stenting of biliary strictures in chronic pancreatitis: a prospective follow-up study. Am J Gastroenterol 2003;98:2448–2453.

[202] Catalano MF, Linder JD, George S et al. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. Gastrointest Endosc 2004;60:945–952.

[203] Farnbacher MJ, Rabenstein T, Ell C et al. Is endoscopic drainage of common bile duct stenoses in chronic pancreatitis up-to-date? Am J Gastroenterol 2000;95:1466–1471.

[204] Vitale GC, Reed DN Jr, Nguyen CT et al. Endoscopic treatment of distal bile duct stricture from chronic pancreatitis. Surg Endosc 2000;14:227–231.

[205] Hammel P, Couvelard A, O'Toole D et al. Regression of liver fibrosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct. N Engl J Med 2001;344:418–423.

[206] Barthet M, Bernard JP, Duval JL et al. Biliary stenting in benign biliary stenosis complicating chronic calcifying pancreatitis. Endoscopy 1994;26:569–572.

[207] Tabibian J, Asham E, Goldstein L et al. Endoscopic treatment with multiple stents for post-liver-transplantation nonanastomotic biliary strictures. Gastrointest Endosc 2009;69:1236–1243.

[208] Kiehne K, Fölsch UR, Nitsche R. High complication rate of bile duct stents in patients with chronic alcoholic pancreatitis due to noncompliance. Endoscopy 2000;32:377–380.

[209] Cahen DL, Rauws EA, Gouma DJ et al. Removable fully covered self-expandable metal stents in the treatment of common bile duct strictures due to chronic pancreatitis: a case series. Endoscopy 2008;40:697–700.

[210] Behm B, Brock A, Clarke BW et al. Partially covered self-expandable metallic stents for benign biliary strictures due to chronic pancreatitis. Endoscopy 2009;41:547–551.

[211] van Berkel AM, Cahen DL, van Westerloo DJ et al. Self-expanding metal stents in benign biliary strictures due to chronic pancreatitis. Endoscopy 2004;36:381–384.

[212] Deviere JM, Reddy DN, Puspok A et al. Preliminary results from a 187 patient multicenter prospective trial using metal stents for treatment of benign biliary strictures. Gastrointest Endosc 2012;75: AB123.

[213] Avula H, Sherman S. What is the role of endotherapy in chronic pancreatitis? Therap Adv Gastroenterol 2010;3:367–382.

[214] Maire F, Sauvanet A. Palliation of biliary and duodenal obstruction in patients with unresectable pancreatic cancer: endoscopy or surgery? J Visc Surg 2013;150(3 Suppl):S27–S31.

[215] Madrigal E, Chennat J. Endoscopic Management of Pancreatic Cancer: from Diagnosis to Palliative Therapy. In: Srivastava S. (ed.) Pancreatic Cancer – Clinical Management, Rijeka: InTech, 2012, pp. 213–236.

[216] Artifon ELA, Sakai P, Cunha JEM et al. Surgery or endoscopy forpalliation of biliary obstruction due to metastatic pancreaticcancer. Am J Gastroenterol 2006;101:2031–2037.

[217] Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006;02:CD004200.

[218] Moss AC, Morris E, Leyden J et al. Malignant distal biliary obstruction: a systematic review and meta-analysis ofendoscopic and surgical bypass results. Cancer Treat Rev 2007;33:213–221.

[219] Chandrasegaram MD, Eslick GD, Mansfield CO et al. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction. Surg Endosc 2012;26:323–329.

[220] Jeurnink SM, Polinder S, Steyerberg EW, Kuipers EJ, SiersemaPD. Cost comparison of gastrojejunostomy versus duodenalstent placement for malignant gastric outlet obstruction. J Gastroenterol 2010;45:537–543.

[221] Kneuertz PJ, Cunningham SC, Cameron JL et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned froma large, single institution experience. J Gastrointest Surg 2011;15:1917–1927.

[222] Fiori E, Lamazza A, Volpino P et al. Palliative management of malignant antro-pyloric strictures Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res 2004;24:269–271.

[223] Rudolph HU, Post S, Schlüter M, Seitz U, Soehendra N, Kähler G. Malignant gastroduodenal obstruction: retrospective comparison of endoscopic and surgical palliative therapy. Scand J Gastroenterol 2011;46:583–590.

[224] Arguedas MR, Heudebert GH, Stinnett AA, Wilcox CM. Biliary stents in malignant obstructive jaundice due to pancreatic carcinoma: a cost-effectiveness analysis. Am J Gastroenterol 2002;97:898–904.

[225] Rogart JN. The plastic biliary stent: an obsolete device for managing pancreatic cancer? J Clin Gastroenterol 2010;44:389–390.

[226] Wasan SM, Ross WA, Staerkel GA, Lee JH. Use of expandable metallic biliary stents in resectable pancreatic cancer. Am J Gastroenterol 2005;100:2056–2061.

[227] Chen VK, Arguedas MR, Baron TH. Expandable metal biliary stents before pancreaticoduodenectomy for pancreatic cancer: a Monte-Carlo decision analysis. Clin Gastroenterol Hepatol 2005;3:1229–1237.

[228] Boulay BR, Gardner TB, Gordon SR. Occlusion rate and complications of plastic biliary stent placement in patients undergoing neoadjuvant chemoradiotherapy for pancreatic cancer with malignant biliary obstruction. J Clin Gastroenterol 2010;44:452–455.

[229] Rogart JN, Boghos A, Rossi F et al. Analysis of endoscopic management of occluded metal biliary stents at a single tertiary care center. Gastrointest Endosc 2008;68:676–682.

[230] Yeoh KG, Zimmerman MJ, Cunningham JT et al. Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. Gastrointest Endosc 1999;49:466–471.

[231] Artifon EL, Aparicio D, Paione JB et al. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. J Clin Gastroenterol 2012;46:768–774.

[232] Dhir V, Artifon EL, Gupta K et al. Multicenter study on endoscopic ultrasound guided expandable biliary metal stent placement: choice of access route, direction of stent insertion, and drainage route. Dig Endosc. 2014; 26:430-435.

[233] Khashab MA, Valeshabad AK, Modayil R et al. EUS-guided biliary drainage by using a standardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques (with videos). Gastrointest Endosc 2013;78:734–741.

[234] Varadarajulu S, Banerjee S, Barth B et al. Enteral stents. Gastrointest Endosc 2011;74:455–464.

[235] Kim KO, Kim TN, Lee HC. Effectiveness of combined biliary and duodenal stenting in patients with malignant biliary andduodenal obstruction. Scand J Gastroenterol 2012;8–9:962–967.

[236] Costamagna G, Alveras P, Palladino F et al. Endoscopic pancreatic stenting in pancreatic cancer. Can J Gastroenterol.1999;13;481–487.

[237] Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc 1996;44:656–662.

[238] Ramesh J, Varadarajulu S. Interventional endoscopic ultrasound. Dig Dis 2008;26:347–355.

[239] Penman ID, Rösch T. EUS 2008 Working Group document: evaluation of EUS-guided celiac plexus neurolysis/block (with video). Gastrointest Endosc 2009;69: S28–S31.

[240] Wyse JM, Carone M, Paquin SC et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 2011;29:3541–3546.

[241] Arcidiacono PG, Calori G, Carrara S et al. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev 2011;(3):CD007519.

[242] Ascunce G, Ribeiro A, Reis I et al. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). Gastrointest Endosc 2011;73:267–274.

[243] LeBlanc JK, Al-Haddad M, McHenry L et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? Gastrointest Endosc 2011;74:1300–1307.

[244] Doi S, Yasuda I, Kawakami H, Hayashi T et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy 2013;45:362–369.

[245] Gan SI, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc 2005;61:746–752.

[246] DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc 2009;70:710–723.

[247] DeWitt J, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. Gastrointest Endosc 2010;72:862–866.

[248] Oh HC, Seo DW, Lee TY et al. New treatment for cystic tumors of the pancreas: EUS guided ethanol lavage with paclitaxel injection. Gastrointest Endosc 2008;67:636–642.

[249] Oh HC, Seo DW, Song TJ et al. Endoscopic ultrasonography-guided ethanol lavage with aclitaxel injection treats patients with pancreatic cysts. Gastroenterology 2011;140:172–179.

[250] DiMaio CJ, DeWitt JM, Brugge WR. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. Pancreas 2011;40:664–668.

[251] Levy MJ, Thompson GB, Topazian MD et al. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc 2012;75:200–206.

[252] Jürgensen C, Schuppan D, Neser F et al. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc 2006;63:1059–1062.

[253] Deprez PH, Claessens A, Borbath I et al. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. Acta Gastroenterol Belg 2008;71:333–337.

[254] Giovannini M. Concentration-dependent ablation of pancreatic tissue by EUS-guided ethanol injection. Gastrointest Endosc 2007;65:278–280.

[255] Wallace MB, Sabbagh LC. EUS 2008 Working Group document: evaluation of EUS-guided tumor ablation. Gastrointest Endosc 2009;69: S59–S63.

[256] Chang KJ, Nguyen PT, Thompson JA et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer 2000;88:1325–1335.

[257] Hecht JR, Bedford R, Abbruzzese JL et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res 2003;9:555–561.

[258] Irisawa A, Takagi T, Kanazawa M et al. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. Pancreas 2007;35:189–190.

[259] Hecht JR, Farrell JJ, Senzer N et al. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc 2012;75:332–338.

[260] Hanna N, Ohana P, Konikoff FM et al. Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. Cancer Gene Ther 2012;19:374–381.

[261] Klapman JB, Chang KJ. Endoscopic ultrasound-guided fine-needle injection. Gastrointest Endosc Clin N Am 2005;15:169–177, x.

[262] Chang KJ. EUS-guided fine needle injection (FNI) and anti-tumor therapy. Endoscopy 2006;38 Suppl 1:S88–S93.

[263] Verna EC, Dhar V. Endoscopic ultrasound-guided fine needle injection for cancer therapy: the evolving role of therapeutic endoscopic ultrasound. Therap Adv Gastroenterol 2008;1:103–109.

[264] Kim HJ, Seo DW, Hassanuddin A et al. EUS-guided radiofrequency ablation of the porcine pancreas. Gastrointest Endosc 2012 Nov;76(5):1039–1043.

[265] Varadarajulu S, Jhala NC, Drelichman ER. EUS-guided radiofrequency ablation with a prototype electrode array system in an animal model (with video). Gastrointest Endosc 2009 Aug;70(2):372–376.

[266] Gaidhane M, Smith I, Ellen K et al. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the pancreas in a porcine model. Gastroenterol Res Pract 2012;2012:Art. ID 431451.

[267] Arcidiacono PG, Carrara S, Reni M et al. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. Gastrointest Endosc 2012;76:1142–1151.

[268] Sun S, Xu H, Xin J et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy 2006;38:399–403.

[269] Jin Z, Du Y, Li Z et al. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy 2008;40:314–320.

[270] Chang KJ, Lee JG, Holcombe RF et al. Endoscopic ultrasound delivery of an antitumor agent to treat a case of pancreatic cancer. Nat Clin Pract Gastroenterol Hepatol 2008;5:107–111.

[271] Ammar T, Cote GA, Creach KM et al. Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. Gastrointest Endosc 2010;71:630–633.

[272] Park WG, Yan BM, Schellenberg D et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. Gastrointest Endosc 2010;71:513–518.

[273] Sanders MK, Moser AJ, Khalid A et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointest Endosc 2010;71:1178–1184.

[274] Khashab MA, Kim KJ, Tryggestad EJ et al. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointest Endosc 2012;76:962–971.

Chapter 9

New Developments in Endoscopy

Arjuna P. De Silva

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60544

Abstract

The small bowel remains the "last frontier" in gastroenterology for a long period after the start of endoscopy. Even with the advent of better endoscopes and colonoscopies barium meal and follow through remained the preferred method of investigation of the small bowel. Although push enteroscopy was present from the 1980's it was not until the advent of device assisted enteroscopy that the small bowel was finally conquered. Device assisted enteroscopy includes, double balloon enteroscopy, single balloon enteroscopy and spiral enteroscopy. The other method of visualizing the small bowel was capsule enteroscopy. Capsule enteroscopy too revolutionized endoscopy as it gave patients a degree for freedom never before enjoyed and would be the best screening tool available. However, its main disadvantage remains the inability to obtain biopsies.

Keywords: Enteroscopy, small bowel, double ballon, single balloon, spiral enteroscopy, capsule enteroscopy

1. Introduction

1.1. Imaging the small bowel – The last frontier

The small bowel has remained the "last frontier" in gastroenterology for a long period after the start of endoscopy. Even with the advent of better endoscopes and colonoscopies. Barium meal and follow through remained the preferred method of investigation of the small intestine for many years [1]. This however, was inconvenient, exposed the patient to unwanted radiation and provided poor quality pictures. In a way it was similar to the back and white television of

old. Other methods include computed tomography (CT) enteroclysis or enterography,magnetic resonance enteroclysis or enterography and small bowel ultrasound.

One reason for this delay in finding a proper modality for imaging the small intestine maybe the fact that small intestinal tumours are much less common than colonic polyps[2]. Thus the need for the procedure may not have been as urgent as it was for say colonic investigation. However, during the last ten years this "last frontier" has been well and truly conquered. Balloon enteroscopy, and capsule endoscopy have revolutionized the investigation of small bowel disorders. In this chapter we will discuss the various methods and their advantages and disadvantages. Although push enteroscopy has been around since the 80's the real break through was after the onset of device assisted enteroscopy.

2. Enteroscopy

Enteroscopy is the act of passing an endoscope beyond the second part of the duodenum and examining the small intestine. It can be divided into push enteroscopy(PE) and device assisted enteroscopy (DAE). Although push enteroscopy has been around since the 1980's this did not allow the full visualization of the small bowel and was very difficult for the patient. This was mainly due to excessive looping of the scope in the small intestine. The length of a PE ranges from about 220 cm to 250 cm and is inserted per orally [3]. This was used occasionally, mainly to try to visualize occult bleeding from the gastrointestinal tract. Enteroscopy was revolutionized by the discovery of DAE the first of which was double balloon enteroscopy (DBE) which, allowed full visualization of the entire small intestine [4]. Subsequently more methods of enteroscopy have been introduced. These are single balloon enteroscopy (SBE) and spiral enteroscopy(SE). With the use of DAE not only has complete visualization of the small intestine been possible, various therapeutic procedures like polypectomy, dilatation or treatment of bleeding hitherto possible only with surgery or laparoscopy could also be performed. This was truly a revolution in gastroenterology.

3. DAE

3.1. Double Balloon (DUB)

Double balloon was first developed in 2001 by Professor Hironori Yammamoto [5]. The system has an endoscope of with an outer diameter of 8.5 mm and a working length of 200cm. It has a soft over tube of 145cm with a 12.2 mm outer diameter and a separate pump. Air insufflation or carbon dioxide is used. Carbon dioxide is recommended as it results in less distension post procedure.

Preparation for the procedure is the same as for a regular colonoscopy. Which will include overnight fasting for solids and the consumption of 4 liters of polyethylene glycol preparation. This is usually consumed in as a split preparation. That is two liters consumed the previous night and the other two liters consumed the next morning.

http://dx.doi.org/10.5772/60544

One balloon is attached to the tip of the scope and the other to the end of the scope [6]. The procedure can be done in an anterograde (oral) or retrograde (anal) method. The endoscope and the over tube is first advanced as far as possible, then the balloon on the over tube is inflated to fix the over tube. Then the endoscope is further advanced as far as possible. Next the balloon on the over tube is deflated and the over tube is advanced up to the inflated tip of the endoscope. The balloon on the over tube is also inflated. Then both endoscope and over tube are with drawn thus, pleating the small intestine. This maneuver is repeated till the scope cannot be advanced any further. At this point the intestine is tattooed using India ink. Then the procedure is repeated in a retrograde manor. The ileum is crossed as would be done during a normal colonoscopy. Thus complete visualization of the small bowel is achieved.

This procedure could take from 70 minutes to 120 minutes. According to guidelines the patient should receive proprofol anesthesia [7]. Fluoroscopy is useful during the learning phase but is not essential. During the learning curve two operators are used. However, later a single operator should suffice. Using the therapeutic channel of the enteroscope most therapeutic procedures that can be performed with a normal upper gastro intestinal endoscope can be done using the enteroscope. This makes it a very useful tool. Although this is relatively safe procedure the complication do occur and will obviously depend on the experience of the operator. The perforation rate is about 0.4 % which can increase to 3% if dilatation is attempted. Other complications include pancreatitis (0.3%), this can be reduced if the balloon is inflated after passing the papilla [8].

3.2. Single balloon enteroscopy(SBE)

Single balloon enteroscopy was introduced in 2007. It uses an enteroscope with a 200cm working length and 2.8 mm channel diameter. The over tube has a diameter of 13.2 and a silicon balloon with a separate pump(figure 1). The technique is the same as for DBE. However, the tip of the balloon is used to anchor the enteroscope to the intestine. Thus there is only one balloon. This makes SBE faster than DBE, Generally it can be used with one operator. As for other types of enteroscopy anesthesia with propofol is the preferred type of anesthesia. Like in DBE both the anterograde and retrograde approaches are used depending on the requirement. Therapeutic procedure are similar with using the SBE. In addition to the speed and simplicity of the procedure the other advantages of the SBE are the fact that is has variable stiffness. Thus eliminating the need for a stiffing wire. It also can be used on patients who have latex allergy. However, it has a lower rate of complete enteroscopy when compared to DBE in most studies.

3.3. Spiral Enteroscopy (SE)

Spiral enteroscopy was introduced in 2008. It has a 118 cm Endo-EaseDiscovery ™ SB overtube with a internal diameter of 9.8mm with a softraised helix, a coupling device to fix to the lubricated overtube to theenteroscope 25 cm from its tip. It has two handles for manual rotation andan injection port for lubrication [9]. Clock wise rotation pleats the smallintestine into the scope, once engaged and advances the same thustransforming the torching force into a linear force. The push and rotatetechnique is used till it passes the ligament of Trietz. After that

Figure 1. SBE with sheath

rotation isonly used. The mesentery of the small bowel prevents it from getting twisted. Like in both DBE and SBE proprofol anesthesia is recommended.Two operators are used for the procedure. One to operate the overtube andthe other to use the scope. Withdrawal is by anti clockwise rotation. Themean time for the procedure is about 34 minutes[10].The major advantages of SE is the speed of insertion and the fact that itdoesn't need extra equipment like a pump. Also the overtube can bedisengaged from the coupler enabling the enteroscope to be withdrawn without loosing the position in the small intestine. This is particularly useful in removing multiple polyps.The overall complication rate is about 0.3% with a perforation rate of 0.4 %The rate of pancreatitis seems lower than in DBE and SBE. So SE seems a useful tool to examine the small bowel as well.

4. Video Capsule Endoscopy (VCE)

The invention of the capsule endoscopy system about 15 years ago once again changed the imaging of the small bowel for ever, giving clear imaging for the first time. Not only is less invasive than endoscopy it gave pictures similar in quality as well. Capsule endoscopy system consists of the wire less capsule which has video camera a sensing system (this includes sensing belt, a data recorder unit, a battery pack and a real time viewer) and a personal computer work station(figure 2). The work station is equipped with manufactures soft ware that offers various functions (localization system, colour enhancement systems, blood detector, quick viewer, scoring system, image atlas) this can help the examiner in reviewing and interpreting the images(11). There are various VCE systems. The capsules themselves and the picture quality has been advancing rapidly.

http://dx.doi.org/10.5772/60544

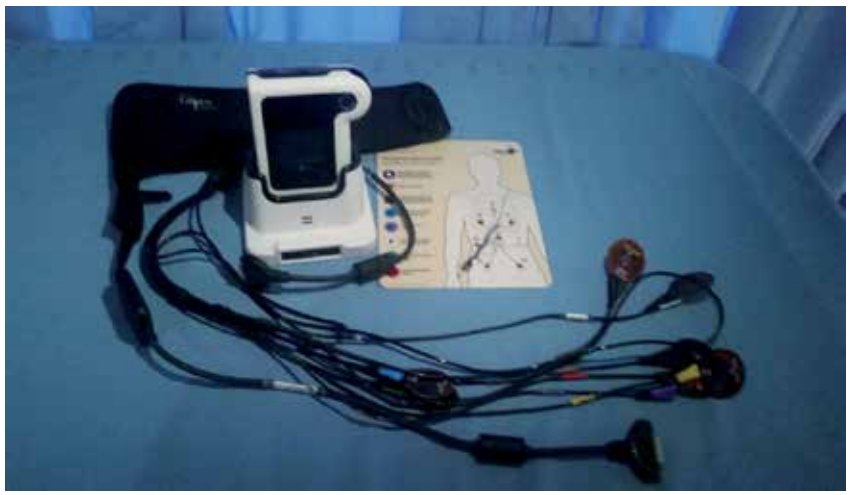

Figure 2. Video capsule recording system

One of the main contraindications for VCE would be suspected intestinal obstruction, strictures, fistulas and as this may result in capsule retention.

The incidence of capsule retention is about 1.4% [12]. VCE is also generally not performed with patients with cardiac pacemakers due to the possibility of interference with these devices. Pregnancy is another contraindication due to the lack of safety data.

Preparation before endoscopy, overnight fast for solids and the consumption of clear liquids only coupled with two liters of poly ethylene glycol (PEG). Although the use of PEG is not compulsory, the consensus is to use it. Generally about 80% of the patients have a complete examination of their small bowel.

Common indications for VCE include, obscure gastrointestinal (GI) bleeding, Crohn's disease, coeliac disease and suspected small intestinal polyps. Of these indications the most commonly used indication would be occult GI bleeding.

One of the biggest disadvantages of the capsule is that currently there is no possibility of taking biopsies or applying any therapeutic procedure to the small intestine. Currently there are some capsules have some degree of maneuverability. Also there is a capsule that does not need the patient to wear any external devices at all. However, this capsule needs to be retrieved to access the data. Future VCE should be able to overcome the disadvantage of inability to take biopsies as currently research and development of a capsule with therapeutic capabilities are underway [13].

5. Conclusion

Due to the patient friendly nature of the examination ideally capsule endoscopy is used in tandem with balloon enterosocopy. This is because currently one of the main disadvantage of

VCE is the lack of the ability to take biopies and to deliver therapy. Also the VCE can give an indication of whether to start the DAE in an anterograde or retrograde direction. When comparing DBE, SBE and SE all are similar although SBE and SE are more simple DBE results in more complete examination of the small intestine.

Device assisted enteroscopy and capsule endoscopy when used in tandem can provide the gastroenterologist with a previously unimaginable access to the small bowel. To the patient it provides hope and comfort that was never before available. Gastroenterolgist all over eagerly await the development of maneuverable VCE with therapeutic options. Thus the "last frontier" of gastroenterology the small intestine has been well and truly conquered.

Author details

Arjuna P. De Silva

Address all correspondence to: apdsilva@yahoo.com

Head Department of Medicine Ragama, University of Kelaniya, Sri Lanka

References

[1] Costamagna G,Shah SK,Riccioni ME, Foschia F, Mutignani M, Perri V, Vecchioli A, Brizi MG, Picciocchi A, Marano P. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. *Gastroenterology* 2002;123:999-1005.

[2] Sidhu R, Saunders DS, McAlindon ME, Thompson M. Capsule endoscopy and enteroscopy:modern modalities to investigate the small bowel in paediatrics. Arch Dis Child 2008;93:154-159.

[3] Wilmar A, Rutgeerts P. Push enteroscopy. Technique, depth and yield of insertion. *Gastrointestinal Endosc Clin N Am* 1996;6:759-776.

[4] Sidhu R, Sanders DS, Morris AJ,McAlindon ME. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut* 2008;17:125-136.

[5] Gay G, Delvaux M. Small-bowel endscopy. *Endoscopy* 2008;40:140-146.

[6] Tee HP,How SH, Kaffes AJ. Learning curve for double balloon enteroscopy:Findings from an analysis of 282 proceedures. World J Gastrointest Endosc 2012;4:368-372.

[7] Akyuz U, Pata C, Senkal V, Erzin Y. Is propofol sedation with midazolam induction safe during endoscopic procedures without anesthesiologist? Hepatogastroenterology 2010;8:137-42.

[8] Gerson LB, Tokar J, Chiorean M,Lo S, Decker GA, Cave D, Bouhaidar D, Mishkin D,Dye C,Halusaka O, Leighton JA, Zfass A, Semrad C. Complications associated with double balloon enteroscopy at nine US centers. *Clin Gastroentrol Hepatol* 2009;7:1177-182.

[9] Akerman PA, Agrawal D, Chen W, Cantero D, Avila J, Pangtay J. Spiral enteroscopy: a novel method of enteroscopy by using the Endo-Ease Discovery overtube and a paediatric colonoscope. *Gastrointest Endos* 2009;69:327-332.

[10] Frieling T,Heise J,Sassenrath W, Hülsdonk A, Kreysel C. Prospective comparison between double-balloon enteroscopy and spiral enteroscopy. *Endoscopy* 2010;42:885-888.

[11] Pan G, Wang L. Swallowable wireless capsule endoscopy: progress and technical challenges. *Gastroenterol Res Pract* 2012; 2012: 841691.

[12] Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010; 71: 280-286.

[13] Valdastri P, Quaglia C, Susilo E, Menciassi A, Dario P, Ho CN, Anhoeck G, Schurr MO. Wireless therapeutic endoscopic capsule: in vivo experiment. *Endoscopy* 2008; 40: 979-982.

Head and Neck

Chapter 10

Observation of the Pharynx to the Cervical Esophagus Using Transnasal Endoscopy with Blue Laser Imaging

Kenro Kawada, Tatsuyuki Kawano, Taro Sugimoto, Toshihiro Matsui, Masafumi Okuda, Taichi Ogo, Yuuichiro Kume, Yutaka Nakajima, Katsumasa Saito, Naoto Fujiwara, Tairo Ryotokuji, Yutaka Miyawaki, Yutaka Tokairin, Yasuaki Nakajima, Kagami Nagai and Takashi Ito

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60541

Abstract

Background In 2014, the new transnasal endoscopy with Blue laser Imaging (BLI) has been developed. Aim We present the usefulness of the observation of from the pharynx to the cervical esophagus using transnasal endoscopy with BLI. Patients and Methods This study was conducted between June 2014 and October 2014. During this period, 70 consecutive patients (60 men, 10 women; mean age 67.9 years old) with esophageal or head and neck cancer underwent endoscopic screening at the oropharynx and hypopharynx by transnasal endoscopy with BLI system We performed this endoscopic observation from oral cavity to pharynx before inserting into the cervical esophagus.The visibility of subsites of the hypopharynx and the orifice of the esophagus was evaluated. The extent of the view of hypopharyngeal opening was classified into 3 categories (excellent, good, poor). Then, the diagnostic accuracy of transnasal endoscopy with BLI system was estimated. Our screening is as follows. First, the patient is asked to bow their head deeply in the left lateral position. We put a hand on the back of the patient's head and push it forward. The patient is then asked to lift the chin as far as possible. In order to inspect the oral cavity, we insert an endoscope without a mouthpiece. After observation of the oral cavity, the endoscope was inserted through the nose. When the tip of the endoscope reached caudal to the uvula, the patient opened his mouth wide, stuck his tongue forward as much as possible and made a vocal sound like "ayyy". The endoscopist caused the endoscope to U-turn and observed the oropharynx, in particular the radix linguae (Intra-

oropharyngeal U-turn method). For examination of the hypopharynx and the orifice of the esophagus, the patient is asked to blow hard and puff their cheeks while the mouth remains closed (Trumpet maneuver). Results 8 elderly cases were excluded because they could not perform the adequate ballooning. Finally, 62 cases were investigated. The ballooning the pyriform sinus and posterior wall not only allows accurate assessment of the stretched pharyngeal mucosa but also gives a view of postcricoid subsite and the orifice of the esophagus. The wide endoscopic view of the pharynx was obtained in a series of the procedures (excellent=53/62, 85.4%; good=7/52, 4.5%; and poor=2/62, 7.6%). Among 70 patients, 6 superficial lesions (8.6%) at the oropharynx(n=1) and hypopharynx (n=5) were discovered with BLI system. Mucosal redness, a pale thickened mucosa, white deposits or loss of a normal vascular pattern, well demarcated areas covered with scattered dots are important characteristics to diagnose superficial carcinoma. Conclusion The more progress achieved in transnasal endoscopy rapidly in the last few years, it can improve for observing the blind area using trans-oral endoscopy, therefore the trans-nasal endoscope will be a standard tool for the screening of the upper gastrointestinal tract in the near future.

Keywords: Transnasal endoscopy, Blue laser imaging, Superficial pharyngeal cancer

1. Introduction

According to the "field cancerization" concept [1], head and neck cancer, especially pharyngeal cancer, frequently coexist with esophageal cancer. Recently several reports [2, 3] have indicated the possibility of applying narrow-band imaging (NBI) endoscopy with magnification to improve the detection of superficial pharyngeal cancer. Compared with conventional endoscopy, NBI results in dramatic improvements in the rate detection of superficial lesions and significant enhancement in visualizing the microvascular structure of the mucosal surface [4]. The superiority of NBI was also recently demonstrated in a multicenter randomized controlled trial in Japan [5]. As more progress has been achieved in the field of endoscopy, the number of superficial cancers in the head and neck region has increased.

However, some areas are difficult to observe with transoral endoscopy. In particular, achieving circumferential observation of the hypopharyngeal mucosa is difficult during conventional endoscopy due to the anatomically closed field, effects of the pharyngeal reflex and accumulation of saliva. On conventional endoscopic screening, the physician usually inserts the endoscope from the left pyriform sinus of the hypopharynx to the cervical esophagus, with a blind space in the posterior wall and postcricoid subsite of the hypopharynx as well as radix linguae. Therefore, detecting early signs of cancer in the blind space is difficult for gastrointestinal endoscopists. On the other hand, transnasal endoscopy may be performed comfortably due to attenuation of the gag reflex. In Japan, the transnasal endoscopy is a very popular procedure and can be performed without sedation. It has also been reported that transnasal endoscopy may be performed less invasive with respect to the cardiopulmonary function [6,

http://dx.doi.org/10.5772/60541

7], and the technique is considered to be more comfortable for the patient than conventional endoscopy.

Since we developed the pharyngolaryngeal observation method using transnasal endoscopy in 2009, we have constantly evolved the procedure in order to better detect carcinoma in the head and neck at earlier stages in cases often coexistent with esophageal cancer. In 2014, a new transnasal endoscopy device with Blue laser Imaging (BLI) was developed. The pharynx is the orifice of the gastrointestinal tract. In this article, we present the usefulness of observing the pharynx to the cervical esophagus using transnasal endoscopy with BLI.

2. Simple questionnaire

A complete medical history, including demographic and clinical data, was obtained prior to the endoscopy procedure. Selected patients constituting a high-risk group for pharyngeal carcinoma are beneficial targets of endoscopic surveillance. Epidemiological studies have detected several strong predictors for identifying persons at high risk for pharyngeal and esophageal squamous cell carcinomas. For example, alcohol drinking and tobacco smoking synergistically increase the risk of both cancers [8, 9], as does a reduced intake of greenish-yellow vegetables and fruits [10] and a low body mass index [11]. The presence of distinct esophageal iodine-unstained lesions and melanosis is also associated with a risk of cancer [12, 13], and alcohol consumption combined with inactive aldehyde dehydrogenase-2 (ALDH2) and less active alcohol dehydrogenase (ADH1B) enhances cancer risks in a multiplicative fashion [14, 15]. The detection of an enlarged mean corpuscular volume (MCV) [16], as induced by heavy drinking or smoking, a high level of acetaldehyde exposure, and/or poor nutrition, may be useful for identifying high-risk persons.

The results of a simple flushing questionnaire have been reported to predict the ALDH2 phenotype with a high accuracy [17].

3. Preparation

Transnasal endoscopy was performed without sedation. Prior to commencement of the procedure, each nasal cavity was sprayed with 0.05% naphazoline nitrate to induce vasoconstriction, followed by premedication with 100 mg of dimethylpolysiloxane and 10 000 U of pronase, with sodium bicarbonate to remove mucus and foam in the stomach. Nasal anesthesia was started by spraying a solution of 4% lidocaine into the nostril for three minutes, after which a swab covered with 8 % lidocaine spray was inserted into the deeper nasal cavity for two minutes. The patient was then placed in the lateral decubitus position to receive endoscopy. Antispasmodics such as scopolamine were not used for premedication.

3.1. Equipment

Recently, we applied a new transnasal esophagogastroduodenoscopy (EGD) device [EG-L580NW, Fuji Film, Tokyo, Japan] with the LASEREO system (a video processor (VP-4450:

FUJIFILM Co. Tokyo) including a light source (LL-4450; FUJIFILM Co. Tokyo)) under modification of the endoscopic technique for observing head and neck cancers and obtained excellent results. The endoscope is a transnasal endoscope that can provides high quality endoscopic images to be viewed on a monitor and digitally recorded with a wide field view of 140 degrees. The LASEREO system (FUJIFILM Co. Tokyo) is a novel endoscopic system employing a semiconductor LASER as a light source. This system is equipped with two LASERs with different in a wavelengths, one for white light sources (wavelength: 450 nm), and one for BLI (wavelength: 410 nm). The white light observation mode consists of a 450 nm LASER and fluorescence of white light phosphor, which is excited by a 450 nm LASER. The phosphor exists in the endoscope. BLI observation mode, which consists of a 410 nm LASER and feeble fluorescence light excited by a 450 nm LASER and is useful for acquiring mucosal surface information, including patterns of the surface blood vessels and structures. The endoscope allows for detailed observations in close view, as it has a focal length of 3 mm to achieve good endoscopic images. The endoscope also has a forceps with channel measuring 2.4 mm in diameter, which improves the ability to aspirate saliva and gastric juices and remove gastric mucus adhering to the tip of the endoscope. It has been reported that BLI is useful for making the diagnosis of colorectal tumors [18], or upper gastrointestinal lesions [19]. An abnormal microvascular pattern in brownish areas can be detected in most pharyngeal and esophageal cancers in the near view with white light images and clearly observed on BLI images. The color contrast of pharyngeal and esophageal cancers rises with BLI, resulting in useful screening result.

3.2. Endoscopic examinations-from the oral cavity to the oropharynx

Our screening procedure is as follows. First, the patient is asked to bow their head deeply in the lateral decubitus position. We then place a hand on the back of the patient's head and push it forward. The patient is then asked to lift the chin as far as possible (lateral sniffing position).

In order to avoid overlooking cancers in the floor of the mouth, soft plate and uvula, we first observe the oral cavity (Figure 1). and then insert the endoscope without a mouthpiece and subsequently observe the upper, lateral and posterior wall of the oropharynx while the patient sticks their tongue forward (Figure 2).

After observing the buccal cavity, further oropharyngeal observation is carried out with a retroflexed endoscope inserted via the nose. When the tip of the endoscope reachs the area caudal to the uvula, the patient opens their mouth wide and sticks their tongue forward as much as possible while making a vocal sound similar to "ayyy". The endoscopist causes the endoscope to make a U-turn (intra-oropharyngeal U-turn method) and observes the oropharynx, in particular the radix linguae. A schematic drawing of the procedure is shown in (Figure 3). We previously reported the usefulness of the intra-oropharyngeal U turn method [20]. One hundred and seventy-two patients underwent treatment with this method from April to October 2012. It was possible to observe all areas of the tongue from the radix linguae to the apex linguae, in 160 cases (93%) [21], and a frontal view of the papillae vallatae was obtained in all patients (Figure 4). After completing the intra-oropharyngeal U-turn method, the tip of the endoscope is inserted gently between the epiglottis and the tongue to observe the vallecula and the tonsil side of the epiglottis.

http://dx.doi.org/10.5772/60541

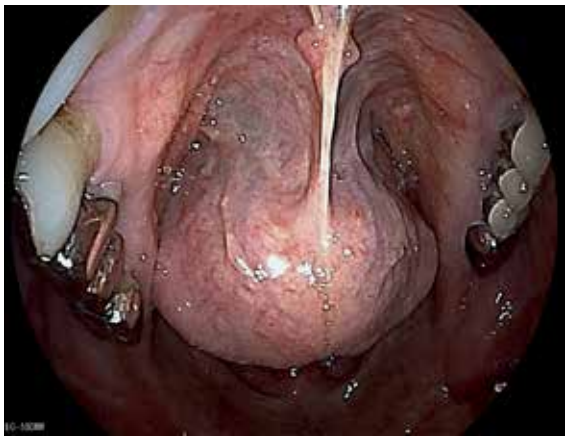

Figure 1. A view of the floor of the mouth through a trans-oral approach.

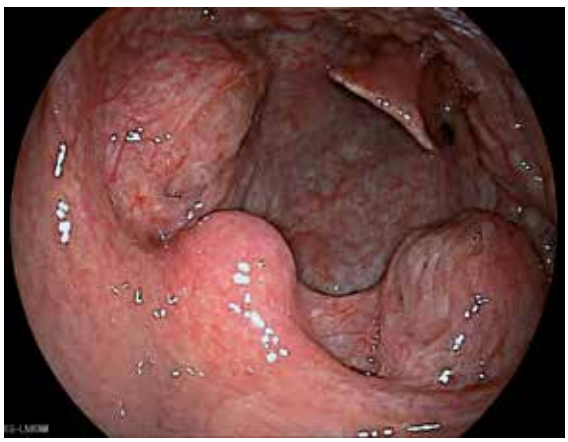

Figure 2. A view of the oropharynx through a trans-oral approach.

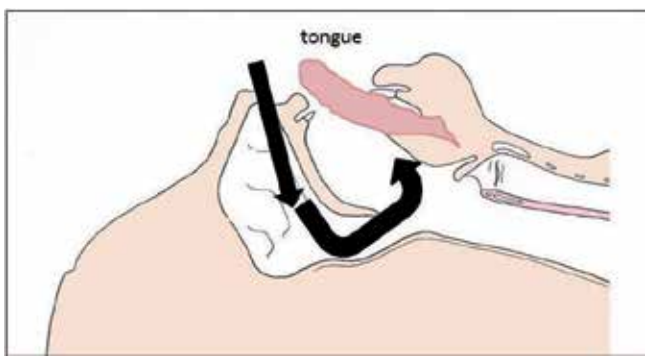

Figure 3. Schema of intra-oropharyngeal U-turn method.

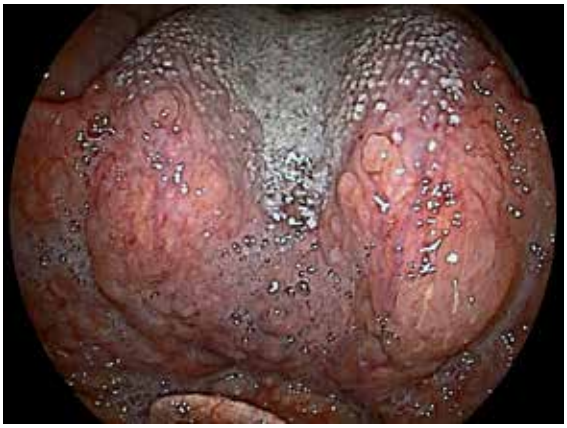

Figure 4. A view of the radix linguae through a trans-nasal approach.

3.3. Endoscopic examination from the hypopharynx to the cervical esophagus

The vocal cords and right and left pyriform sinus should be observed (Figure 5). When the patient vocalizes, the vocal cords move to the anterior region, making observation of the pyriform sinus easier. The technique of esophagogastroduodenoscopy (EGD) has also been improved, although it is not possible to observe otorhinolaryngeal sites in some patients due to the gag reflex. The postcricoid subsite and orifice of the esophagus are especially difficult to visualize using flexible laryngopharyngoscopy. Several reports have suggested techniques for improving the view of the hypopharynx with a flexible fiber optic laryngoscope. Spraggs and Harris described a modified Valsalva technique involving the nose being squeezed shut by the examiner's hand while the patient attempts to blow through the obstructed nose [22, 23]. Other reports have described the trumpet maneuver [24], the anterior neck skin traction maneuver [25] or a combination of the two [26]. However, these maneuvers have not been attempted in conventional EGD due to the effects of the gag reflex.

Since we introduced the modified Valsalva maneuver using transnasal endoscopy in 2009 [27], a total of 94 superficial head and neck cancers were found in 70 patients using transnasal ESD over the last four years [28]. Furthermore, it has been reported the modified Valsalva maneuver using transnasal endoscopy is prospectively useful for detecting superficial pharyngeal cancer [29].

For the examination of the hypopharynx and orifice of the esophagus, the patient is asked to blow hard and puff their cheeks while keeping their mouth closed. The endoscopist pulls the patient's chin forward with the right hand, and the characteristics of the posterior wall of the hypopharynx and postcricoid subsite pharyngeal wall enable the pharyngeal mucosa to be stretched out and the postcricoid region (Figure 6) and orifice of the esophagus to be visualized in an open space. The transnasal BLI system enables clear visualization of the palisade vessels of the pharyngoesophageal junction (Figure 7). The total time required to perform the procedure is approximately two minutes. This technique is easy to perform and feasible in almost all high-risk patients. The endoscope is then passed into the cervical esophagus.

http://dx.doi.org/10.5772/60541

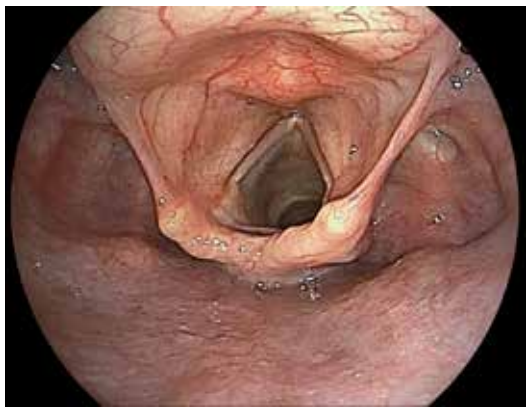

Figure 5. A view of the larynx and the hypopharynx.

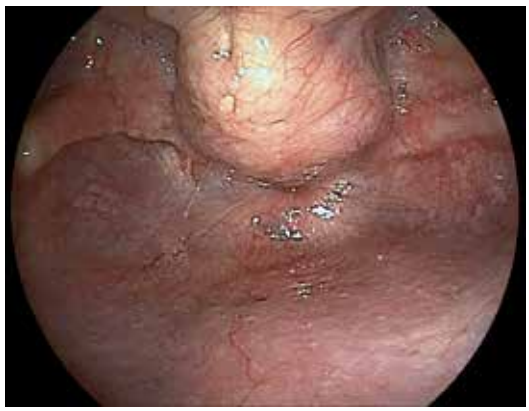

Figure 6. Transnasal endoscopy using trumpet maneuver improves the visualization of the hypopharynx and the pharyngoesophageal junction.

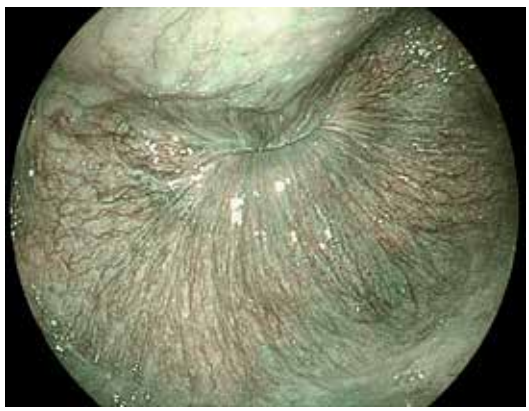

Figure 7. The endoscopic image of the pharyngoesophageal junction using Blue lasar imaging (BLI).

4. Patients and Methods

This study was conducted between June 2014 and October 2014. During this period, 70 consecutive patients (60 males, 10 females; mean age: 67.9 years old) with esophageal or head and neck cancer underwent endoscopic screening of the oropharynx and hypopharynx using transnasal endoscopy with the BLI system at the Department of Esophageal and General Surgery, Tokyo Medical and Dental University. We performed endoscopic observation from the oral cavity to pharynx before inserting the endoscope into the cervical esophagus. BLI images were obtained on a color video monitor by pushing a fingertip control switch. The visibility of subsites of the hypopharynx and the orifice of the esophagus was evaluated, and the extent of view of the hypopharyngeal opening was classified into three categories (excellent, good, poor). The diagnostic accuracy of transnasal endoscopy with the BLI system was subsequently estimated. Two experienced endoscopists (K.K., N.F.) performed all of the examinations, using the same endoscope.

The examinations were recorded onto video cassettes. Written informed consent was obtained from all patients prior to the endoscopic examinations.

5. Results

Eight elderly patients were excluded due toinadequate ballooning. Finally, 62 patients were investigated. Ballooning of the pyriform sinus and posterior wall allows for both an accurate assessment of the stretched pharyngeal mucosa and provides a view of the postcricoid subsite and orifice of the esophagus.

A wide endoscopic view of the pharynx was obtained in a series of the procedures (excellent=53/62, 85.4%; good=7/52, 4.5%; and poor=2/62, 7.6%). Among the 70 patients, six superficial lesions (8.6%) at the oropharynx (n=1) and hypopharynx (n=5) were discovered with the BLI system (Table 1). Three lesions were located at the piriform sinus and two lesions were located on the posterior wall of the pharyngoesophageal junction, which in the blind area on conventional screening. A representative lesion is shown in Figure 8. The hypopharynx was stretched according to the trumpet maneuver, whicn allowed us to detect a slightly depressed area. On BLI observation, a well demarcated brownish area was recognized, with scattered brown dots within the areas on a close view (Figure 9). The lesion was resected via endoscopic laryngopharyngeal surgery (ELPS). The area unstained with iodine was similar to the brownish area observed on BLI (Figure 10).

The histopathological examination revealed a diagnosis of squamous cell carcinoma with microinvasion beneath the epithelium (Figure 11).

In one case, superficial oropharyngeal cancer was located at the radix linguae (Figure 12), and the intra-oropharyngeal U-turn method was very effective for making the diagnosis.

http://dx.doi.org/10.5772/60541

Case	Sex	Age	Esophageal cancer	location	Macroscopic type	Size	Treatment	Tumor thickness
1	Male	72	Synchronous	PW	0-IIa	21mm	ELPS	350μm
2	Female	56	Metachronous	PW	0-IIc	12mm	ELPS	250μm
3	Male	69	Metachronous	rtPS	0-IIb	※10mm	-	
4	Male	63	Synchronous	rtPS	0-IIb	※15mm	-	
5	Male	66	Metachronous	ltPS	0-IIb	※15mm	-	
6	Male	60	Metachronous	Oro	0-IIc	※25mm	TORS	

PW=posterior wall of hypopharynx, rtPS= right piriform sinus
lt PS=left piriform sinus, Oro=oropharynx, TORS=transoral robotic surgery
ELPS=endoscopic laryngopharyngeal surgery ※=endoscopic findings

Table 1. The oropharyngeal and hypopharyngeal cancers detected by transnasal endoscopy with BLI.

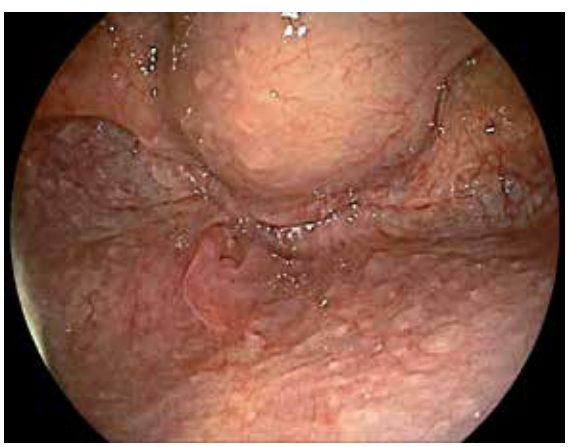

Figure 8. A slightly depressed lesion was observed in the posterior wall of the hypopharynx using the trumpet maneuver.

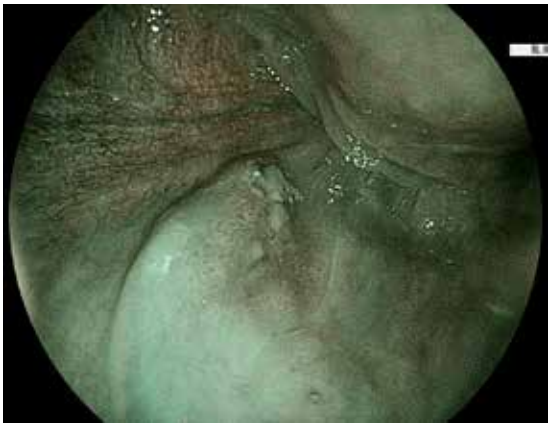

Figure 9. The endoscopic image using the BLI during the trumpet maneuver

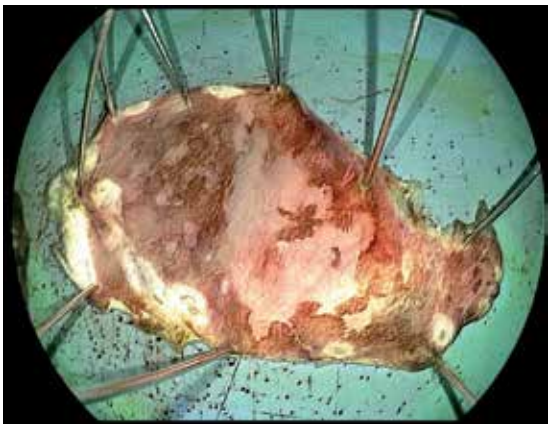

Figure 10. A macroscopic image of the resected specimen.

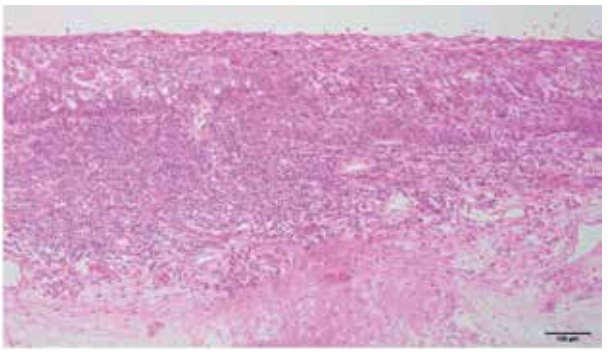

Figure 11. Histopathological examination revealed a diagnosis of squamous cell carcinoma with microinvasion beneath the epithelium.

http://dx.doi.org/10.5772/60541

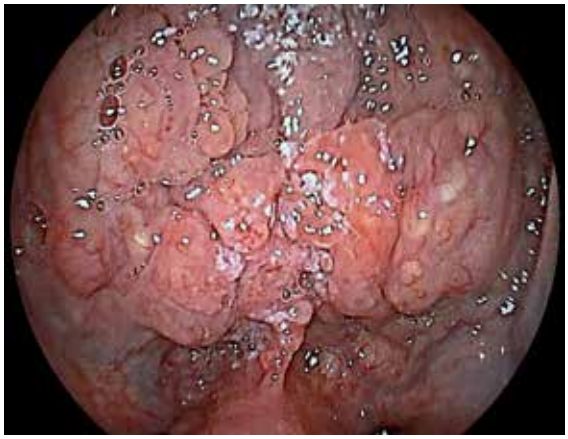

Figure 12. A case of superficial oropharyngeal cancer. The tumor observed using intra-oropharyngeal U-turn method.

5.1. Endoscopic features of superficial pharyngeal cancer

Recent advances in endoscopic procedures, such as magnifying endoscopy and the NBI system, have enabled precise observation of the oropharynx and hypopharynx [2, 5]. Mucosal redness, a pale and thickened mucosal apperance, white deposits and/or loss of the normal vascular pattern are important characteristics for diagnosing superficial carcinoma upon examination under white light (Figure 13). In addition, well demarcated areas covered with scattered dots observed on a closer observation of superficial microvascular structures and allows for the detection of a lesions at an earlier stages. The new transnasal endoscopy procedure with the BLI system enables physicians to easily observe the presence of scattered brown dots, contributing to the diagnosis of superficial cancers (Figure 14). Moreover, close BLI examinations using transnasal endoscopy enable the physician to obtain a mucosal diagnosis, even without magnification.

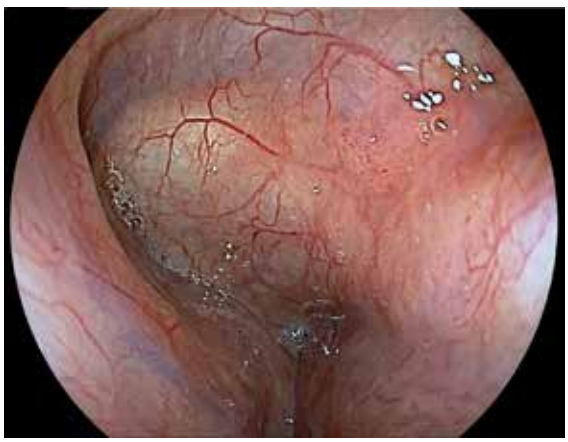

Figure 13. The white light image showed a 0-II b lesion of the right piriform sinus.

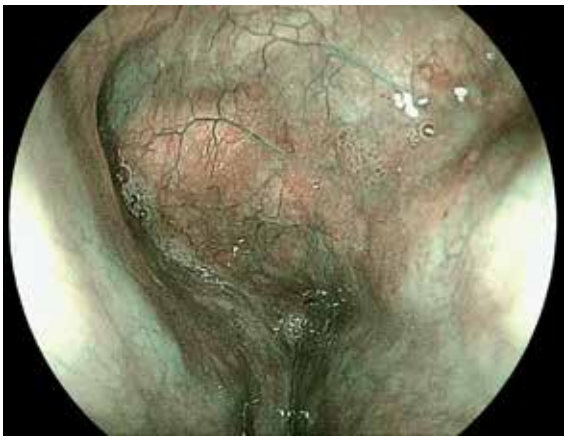

Figure 14. The close BLI image showed brown dots in the 0-II b lesion.

The modified Valsalva maneuver is also useful for detecting proximal invasion of the cervical esophageal cancer. This maneuver helps the physician to determine whether to preserve the patient's voice during surgery. On conventional screening, endoscopic images of hypopharyngeal cancer are often observed, however the distal part of the tumor is not visualized (Figure 15). A BLI endoscopic image obtained during the modified Valsalva maneuver using transnasal ESD is shown in Figure 16. The whole image of the tumor was able to observe (Figure 17). The entire tumor was observed, as indicated in Figure 17: the advanced cervical esophageal cancer had invaded the hypopharynx.

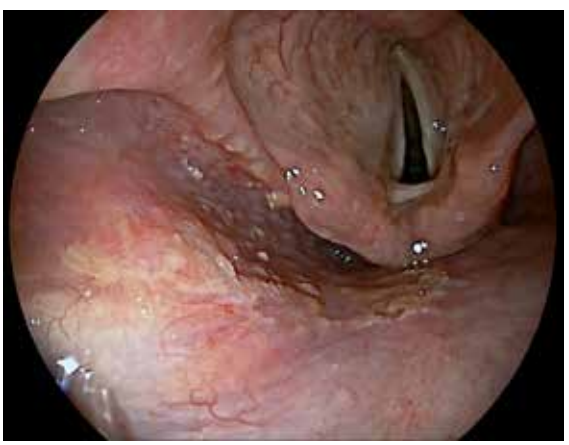

Figure 15. A reddish and irregular mucosa was shown in the hypopharynx. The distal part is not visualized.

http://dx.doi.org/10.5772/60541

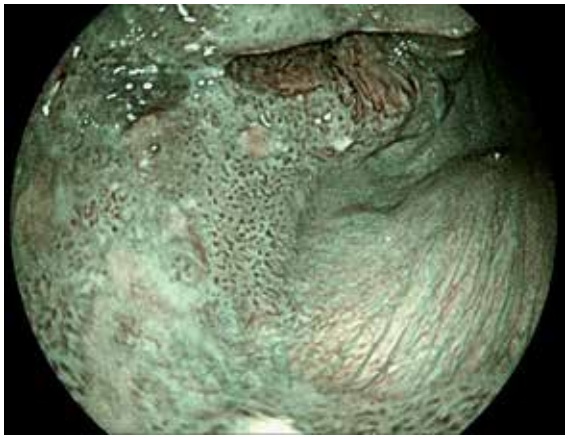

Figure 16. Advanced cancer was observed at the pharyngoesophageal junction using BLI during the trumpet maneuver.

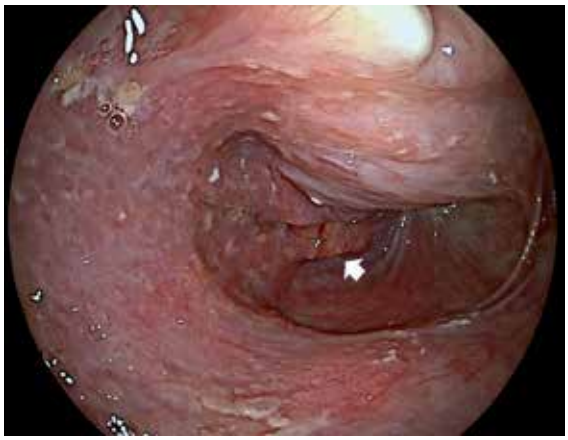

Figure 17. The advanced cervical esophageal cancer had invaded the hypopharynx (arrows).

6. Further research

It has been reported that the application of magnifying endoscopy with the NBI system drastically changes the diagnostic strategy for the early detection of early oropharyngeal and hypopharyngeal cancers. The development of transnasal endoscopy with the BLI system now enables the wider observation and can be used to obtain adequate information for diagnosing early cancers without magnification. The modified Valsalva maneuver and intra-oropharyngeal U-turn method using transnasal endoscopy are not popular in Japan as of yet, however these techniques are very easy to perform, and we expect that this method will become a

standard procedure for observing the pharynx and orifice of the esophagus in the near future. Nevertheless, further studies, including randomized, prospective, multi-institutional joint trials comparing conventional endoscopy with the NBI system or transnasal endoscopy with the BLI system are required.

Transnasal endoscope technology is continually improving. From the viewpoint of early detection of pharyngeal cancer, we hope that transnasal endoscopy will become more widely adopted.

7. Conclusion

The significant progress achieved in the field of transnasal endoscopy rapidly within the last few years has improved the ability to observe the blind area typically noted during conventional screening. Therefore, transnasal endoscopy is expected to become a standard tool for screening of the upper gastrointestinal tract in the near future.

Author details

Kenro Kawada[1*], Tatsuyuki Kawano[1], Taro Sugimoto[2], Toshihiro Matsui[1], Masafumi Okuda[1], Taichi Ogo[1], Yuuichiro Kume[1], Yutaka Nakajima[1], Katsumasa Saito[1], Naoto Fujiwara[1], Tairo Ryotokuji[1], Yutaka Miyawaki[1], Yutaka Tokairin[1], Yasuaki Nakajima[1], Kagami Nagai[1] and Takashi Ito[3]

*Address all correspondence to: kawada.srg1@tmd.ac.jp

1 Department of Esophageal and General Surgery, Tokyo Medical and Dental University, Tokyo, Japan

2 Department of Otorhinolaryngology, Tokyo Medical and Dental University, Tokyo, Japan

3 Department of Human Pathology, Tokyo Medical and Dental University, Tokyo, Japan

References

[1] Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953; 6: 963-968

[2] Muto M, Nakane M, Katada C *et al*. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 2004; 101: 1375-1381.

http://dx.doi.org/10.5772/60541

[3] Watanabe A, Tsujie H, Taniguchi M *et al*. Laryngoscopic detection of pharyngeal carcinoma in situ with narrow band imaging. Laryngoscope 2006; 116: 650-654.

[4] Gono K, Yamazaki K, Doguchi N *et al*. Endoscopic observation of tissue by narrowband illumination. Opt Rev. 2003; 10: 211-215.

[5] Muto M, Minashi K, Yano T, *et al*. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010; 28: 1566-1572.

[6] Kawai T, Miyazaki I, Yagi K, *et al.* Comparison of the effects on cardiopulmonary function of ultrathin transnasal versus normal diameter transoral esophagogastroduodenoscopy in Japan. Hepato-Gastroenterology 2007; 54: 770-774

[7] Mori A, Ohashi N, Maruyama T, *et al*. Cardiovascular tolerance in upper gastrointestinal endoscopy using an ultrathin scope: prospective randomized comparison between transnasal and transoral procedure. Dis Endosc 2008; 20: 79-83

[8] Takezaki T, Shinoda M, Hotta S, *et al.* Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). Cancer Causes Control 2000; 11: 597-608

[9] Zeka A, Gore R, Kriebel D. Effets of alcohol and tabacco on aerodigestive cancer risks:a meta-regression analysis. Cancer Causes Control 2003; 14: 897-906

[10] Yokoyama A, Kato H, Yokoyama T, *et al*. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S- transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 2002; 23: 1851-1859

[11] Yokoyama A, Yokoyama T, Muramatsu T, *et al*. Macrosytosis, a new predictor for esophageal squamous cell carcinoma in Japanese men. Cercinogenesis 2003; 24: 1773-1778

[12] Shimizu Y, Tsukagoshi H, Fujita M, *et al.* Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy 2003; 35: 322-326

[13] Muto M, Takahashi M, Ohtsu A, *et al.* Risk of multiple squamous cell caricinomas both in the esophagus and the head and neck region. Carcinogenesis 2005; 26: 1008-1012

[14] Muto M, Hhitomi Y, Ohtsu A, et al. Association of aldehyde dehydrogenase 2 genepolymorphism with multiple oesophageal dysplasis in head and neck cancer patients. Gut 2000; 47: 256-261.

[15] Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol 2003; 33: 111-121

[16] Yokoyama A, Yokoyama T, Kumagai Y, et al. Mean Corpuscular Volume, Alcohol Flushing and the Predicted risk of squamous cell carcinoma of the esophagus in cancer free Japanese men. Alcohol Clin Exp Res 2005; 29: 1877-1883

[17] Yokoyama T, Yokoyama A, Kato H, et al. Alcohol flushing, alcohol and aldehyde dehydorogenase genotypes, and risk for esophageal squamous cell carcinoma in Japanese men. Cancer Epidermiol Biomark Prev 2003; 12: 1227-1233

[18] Yoshida N, Yagi N, Yanagisawa A, Naito Y. Image-enhanced endoscopy for diagnosis of colorectal tumors in view of endoscopic treatment. *World J. Gastrointest. Endosc.* 4 ; 545-555, 2012

[19] Osawa H, Yamamoto H, Miura Y, et al. Blue laser imaging provides excellent endoscopic images of upper gastrointestinal lesions. Video Journal nad Encyclopedia of GI endoscopy 2014; 1: 607-610

[20] Kawada K, Okada T, Sugimoto T et al. Intraoropharyngeal U-turn method using transnasal esophagogastroduodenoscopy. Endoscopy 46; E137-8, 2014

[21] Kawada K, Okada T, Sugimoto T et al. Intra-oropharyngeal U-turn method with Trans-nasal Endoscopy (in Japanese with English abstract) J.Jpn Bronchoesophagol. Soc., 64:265-270, 2013

[22] Spraggs P D, Harries M L. The modified Valsalva maneuver to improve visualization of the hypopharynx during flexible nasopharyngoscopy. J. Laryngol. Otol. 1995; 109: 863-864.

[23] Purser S, Antippa P. Maneuver to assist examination of the hypopharynx. Head Neck 1995; 17: 389-393.

[24] Hillel AD, Schwartz A N. Trumpet maneuver for visualization and CT examination of the pyriform sinus and retrocricoid area. Head Neck 1989; 11: 231-6.

[25] Colquhoun-Flannery W, Davis A, Carruth J.A.S. Improving the endoscopic view of the hypopharynx with anterior neck traction during the trumpet manoeuvre. J. Laryngol. Otol. 2000; 114: 283-284.

[26] Williams R S, Lancaster J, Karagama Y *et al.* A systematic approach to the nasendoscopic examination of the larynx and pharynx. Clin. Otol. 2004; 29: 175-178.

[27] Kawada K, Kawano T, Nagai K, et al. Transnasal endoscopy for diagnosing superficial oro-hypopharyngeal cancer Stomach and Intestine (in Japanese with English abstract) 2010;45: 228-239

[28] Kawada K, Kawano T, Sugimoto T. Key points and techniques for trans-nasal endoscopic screening for superficial hypopharyngeal cancer. Treatment Strategies Gastroenterology 2013; 2: 42

http://dx.doi.org/10.5772/60541

[29] Tanaka T, Niwa Y, Tajika M, et al. Prospective evaluation of a transnasal endoscopy utilizing flexible spectral color enhancement (FICE) with the Valsalva maneuver for detecting pharyngeal and esophageal cancer. Hepatogastroenterology 2014; 61: 1627-34.

Chapter 11

Minimally Invasive Transcanal Endoscopic Ear Surgery

Lela Migirov and Michael Wolf

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60551

Abstract

Endoscopes have rapidly become widely accepted in the performance of ear surgery. Current chapter describes surgical technique and benefits and limitations for endoscopic eradication of cholesteatoma, endoscopic tympanoplasty, endoscopic stapedotomy and endoscopic cochlear implantation.

Minimally invasive endoscopic and endoscope-assisted surgical techniques are increasingly being employed in the surgical management of cholesteatoma. Endoscopic surgeries distinctly reduced residual cholesteatomas and the indications of later tympanotomy thanks to the good visualization of residual cholesteatoma sites, such as the anterior and posterior epitympanic spaces, sinus tympani, facial recess, and hypotympanum. Minimally invasive transcanal endoscopic approach can be applied as for primary cholesteatomas as well as for revision of CWU cases, when residual/recurrent cholesteatoma is confined to the middle ear, and in CWD or radical cavities, when residual/recurrent disease is hidden in the supratubal recess, sinus tympani or under pseudo-membrane in the large mastoid cavities.

The use of endoscopes in myringoplasty is especially helpful in patients with narrow external canals, anterior defects and bone overhang, when perforation's margins are barely, if at all, visible under a microscope.

The transcanal endoscopic stapedotomy can be beneficial in improving the visibility and accessibility of the stapes and the oval window niche, avoiding manipulation of the chorda tympani nerve and blind fracture of the stapedial crurae.

An endoscopic cochlear implantation involves entering the middle ear by means of endoscopic transcanal tympanotomy and insertion of the electrode array into the scala tympani via the round window under direct endoscopic control. The main benefits of the endoscopic transcanal approach to cochlear implant are improving the visibility

and accessibility of the round window membrane, obviating the need to divide the chorda tympani nerve in order to obtain adequate exposure of the middle ear structures, and eliminating the risk of the facial nerve injury since it is not in the direction of drilling.

Keywords: endoscopic surgery, approach, tympanoplasty, stapedectomy, cochlear implant

1. Introduction

The introduction of endoscopes completely changed the surgical approach to the middle ear pathologies. Management of cholesteatoma continues to pose a surgical challenge, and the choice of surgical technique depends on the extension of the disease, the surgeon's own experience and skills, published data, and the patient's socioeconomic circumstances. Minimally invasive endoscopic and endoscope-assisted surgical techniques are increasingly being employed in the surgical management of cholesteatoma.

2. Endoscopic surgery for cholesteatoma

Exclusive transcanal endoscopic approach (TEA) can be used for the resection of a primary cholesteatoma or for endoscopic revision of an accessible residual/recurrent cholesteatoma in the post-mastoidectomy cavity. In endoscope-assisted ear surgery (EAES), the endoscopes are introduced intraoperatively for completion of surgery performed under a microscope.

Endoscopic ear surgery (EES) and EAES distinctly reduced residual cholesteatomas and the indications of later tympanotomy thanks to the good visualization of residual cholesteatoma sites, such as the anterior and posterior epitympanic spaces, sinus tympani, facial recess, eustachian tube and hypotympanum [1-10]. Moreover, it was found that retraction pockets extending into the facial recess may be more readily removed by using endoscopes than by converting to an intact canal wall mastoidectomy with a facial recess approach [10,11].

The vast majority of cholesteatomas starts to develop in the middle ear and its extensions, and only later involves the mastoid cavity. Thus, the most logical access to a cholesteatoma has not yet advanced to the mastoid is the transcanal approach. However, the endoscopic approach depends on the experience and skills of the surgeon. In addition, otosurgeons are accustomed to using both hands at surgery while in the EES one hand is occupied with the endoscope and the other performs the manipulations for the eradication of the pathology, suctioning, hemostasis and subsequent reconstructions [10].

A cholesteatoma is defined as being accessible with TEA when it does not extend beyond the level of the lateral semicircular canal [11]. In case of cholesteatoma inaccessible even with

http://dx.doi.org/10.5772/60551

angled instruments under direct vision of angled endoscopes traditional mastoidectomy is performed. The optimal surgical approach to residual/recurrent cholesteatoma is a controversial issue since residual lesions can be missed and cholesteatoma tends to recur despite the variety of surgical options. The common sites of residual lesions and recurrences are sinus tympani, attic, anterior epitympanic space, facial recess and the supratubal region, and they can all be visualized and accessed using the TEA [3,5-7,12-26].

Preoperative assessment includes otoscopy and pure tone audiometry in all patients. Recent studies have shown that non-echo planar (non-EPI) diffusion-weighted (DW) magnetic resonance imaging (MRI) can accurately predict the presence and extent of cholesteatoma in both primary and residual cases [27-31]. The size of lesion determined by the non-EPI DW images correlated well with intra-operative findings, with error margins lying within 1 mm [28-31]. Non-EPI DW MRI can distinguish cholesteatoma from other tissues and from mucosal reactions in the middle ear (ME) and mastoid, and it can also demonstrate the extent of the lesion [27-31]. Thus, we prefer performing the non-EPI DWI MRI prior to primary cholesteatoma surgery as well as before revision procedures [31]. Non-EPI DW images allow avoiding the irradiation, and this point is extremely important for all patients, especially children [32]. The choice of approach as in primary as well as in revision surgery depends on the extent of disease and on the preoperative otoscopic and radiological findings (Figures 1-8). We already found that cholesteatoma < 8 mm in size and confined to the ME or its extensions can be eradicated with a minimally invasive TEA, while endoscope-assisted retroauricular mastoidectomy is the preferable procedure for larger lesions [31].

Many primary and some residual/recurrent lesions can be accessed with endoscopes. However, prior to undergoing the intervention, all the patients are informed of the possibility of extending their surgery to a transmastoid approach in the event that the cholesteatoma could not be satisfactorily eradicated by the transcanal endoscopic approach.

2.1. Surgical technique

The operating room setup, instrumentation and surgical technique were similar to those proposed by Tarabichi [11-14]. Rigid 3-mm diameter, 0°, 30° and 45° endoscopes, angled picks and forceps and routine otologic micro-instruments are used for all the TEA procedures (the list of the instruments can be seen in the web site of the International Working Group on Endoscopic Ear Surgery). A wide posterior tympanomeatal flap was elevated via the external auditory canal and then transposed inferiorly in cases of cholesteatoma situated in the middle ear (ME) under a closed or perforated tympanic membrane (TM). If needed, the scutum was removed with a bone curette until the cholesteatoma extension and the mastoid antrum could be visualized. The malleus and incus are removed when they are involved in the cholesteatoma or when they limit access to cholesteatoma in the anterior or posterior epitympanic space. When present, the stapes is left intact and meticulously and gently cleaned when it is involved with the cholesteatoma. Scutumplasty is done with tragal cartilage, and TM defects are reconstructed with the palisade technique and perichondrium in the relevant cases. In certain cases, cholesteatoma can be assessed and removed using the endoscopes directly from the radical cavity or from the mastoid cavity remaining after a canal-wall-down (CWD) procedure.

An operating microscope is used when the surgeon needs both hands to complete the removal of the cholesteatoma from the facial nerve or stapes footplate, and occasionally for ossicular chain reconstruction (OCR). Operative time depends on the extension of the disease, ossicular involvement in cholesteatoma and whether OCR is required.

Post-operative follow-up recommendations included repeated clinical examinations, and all the patients are encouraged to perform non-EPI DWI MRI at approximately one year following surgery. Second-look procedures or secondary OCRs usually are planned according to the clinical and MRI findings and the postoperative audiometric results. Whatever the etiology of cholesteatoma, scutumplasty with cartilage yielded good results in terms of prevention of postoperative retraction pockets.

EES has several advantages as compared to traditional mastoidectomy. This is a minimally invasive surgical approach in terms of incision, bleeding, drilling, postoperative pain and healing, and it is curative in terms of the radical eradication of the pathology including hidden areas poorly accessible and thus overlooked by a microscope. In the TEA, bony work can be circumvented leading to a decrease of possible intraoperative complications. This is functional surgery since scutumplasty and reconstruction of the tympanic membrane lead to conditions favorable to the introduction of the water into the external auditory meatus, and primary ossicular chain reconstruction can be done at the same setting. The patient can be discharged on the same day or on the day after surgery, and the hospital stay can be shortened compared to at least 2 days postoperative admission for uneventful retroauricular mastoidectomy. In contrast to mastoidectomy, the EES can be performed under local anaesthesia, and there is no need for postoperative wound care. Post-EES healing time is usually painless and is shorter compared to mastoidectomy. The set-up time and costs of the endoscopic procedure are comparable with mastoidectomy and even less since there is no need in drilling, cotton material and cauterization for hemostasis, suturing of the wound, bandage and postoperative wound care. The endoscopes and video-cameras are in routine use for endoscopic sinus surgery and thus are already available in most departments. The routine otologic micro-sets should be completed with some angled picks and forceps.

Although mastoidectomy is a procedure that is familiar to all otosurgeons, it can be complicated by accidental trauma to middle cranial fossa dura, dural exposure in the tegmen and sinodural angle, and brain herniation into the mastoid cavity. Dural and tegmen defect due to dural tears and cerebrospinal fluid leakage may result in pneumocephalus, brain herniation, subdural empyema, epidural or brain abscess [33-39]. In addition to primary cholesteatoma cases, minimally invasive TEA can be applied for revision of canal-wall-up (CWU) cases, when residual/recurrent cholesteatoma is confined to the middle ear, and in CWD or radical cavities, when residual/recurrent disease is hidden in the supratubal recess, sinus tympani or under pseudo-membrane in the large mastoid cavities, when access to cholesteatoma via external ear canal is difficult using the operating microscope due to the limited axis of work [24]. The TEA can be one of the options for eradication of residual/recurrent lesions in addition to traditional CWU and CWD techniques. The TEA avoids drilling in the mastoid region, thereby obviating the risk of dural injury and postoperative intracranial complications. Pre-operative non-EPI DWI MRI can predict cholesteatoma extension and is essential in planning revision surgery

http://dx.doi.org/10.5772/60551

for residual/recurrent lesions. Screening with non-EPI DWI MRI at one year postoperatively is highly recommended to rule out residual disease, especially in patients who underwent CWU mastoidectomies.

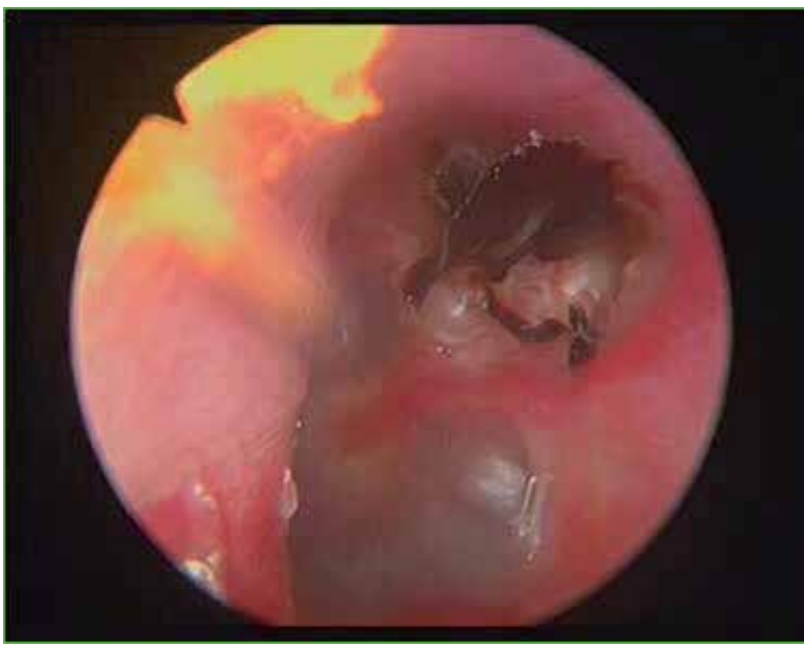

Figure 1. A view (with a 0° endoscope) of a left ear primary retraction pocket cholesteatoma.

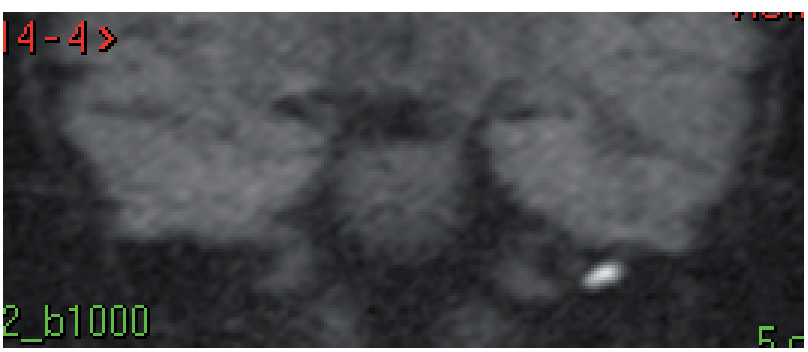

Figure 2. Non-EPI DW coronal images of the same patient presented in Figure 2 shows a 7-mm hyperintense lesion in the left attic (it was managed with TEA).

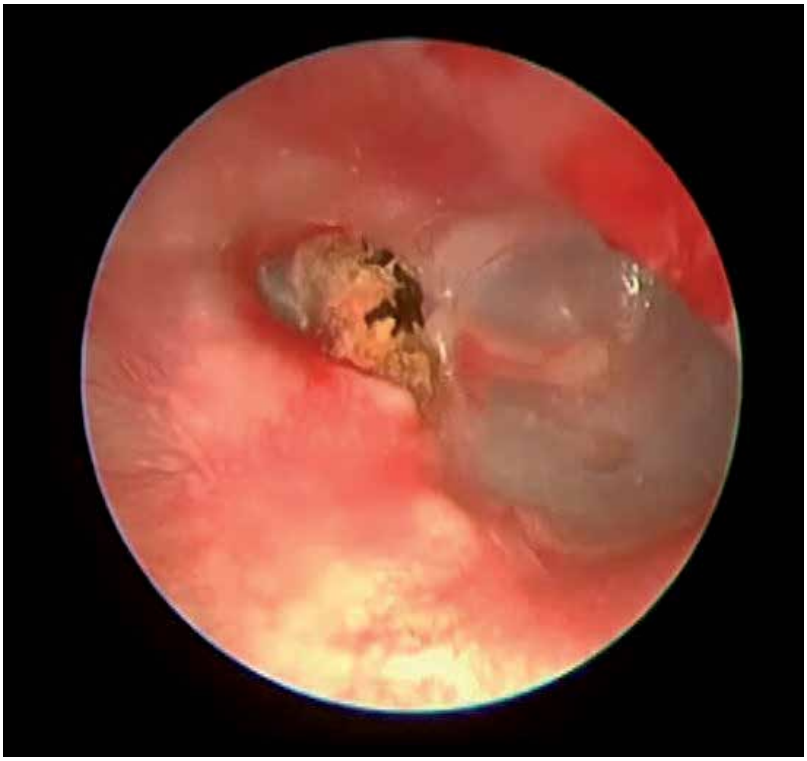

Figure 3. Endoscopic view of right ear primary retraction pocket cholesteatoma extended to the mastoid cavity.

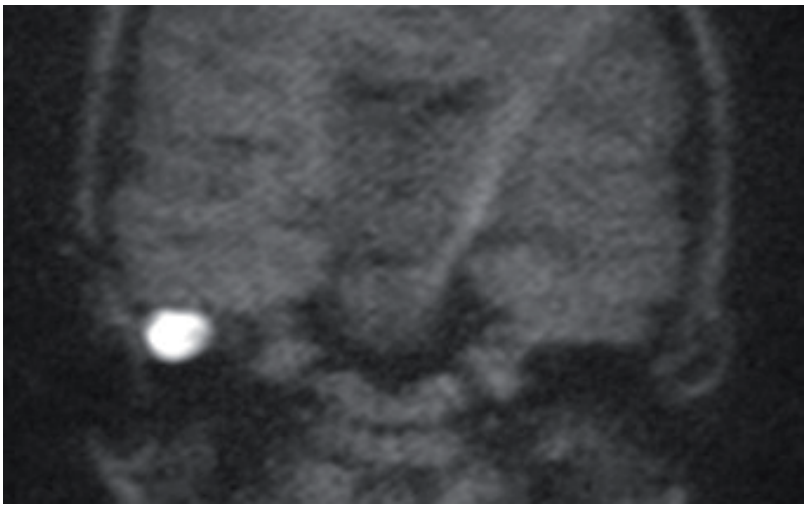

Figure 4. Non-EPI DW coronal images of the same patient presented in Figure 3 shows a hyperintense lesion occupied whole mastoid cavity (it was managed with CWD mastoidectomy).

http://dx.doi.org/10.5772/60551

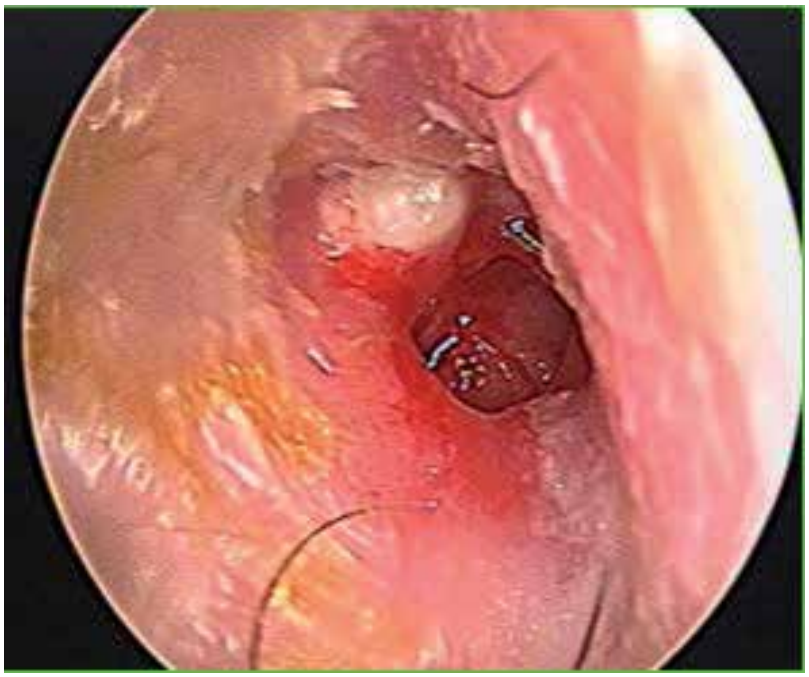

Figure 5. Endoscopic view of right ear residual cholesteatoma presented 1 year after CWU mastoidectomy.

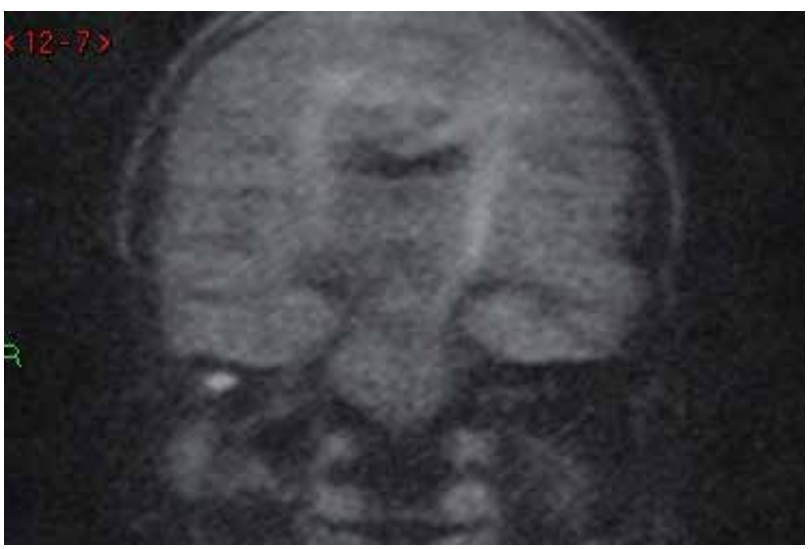

Figure 6. Non-EPI DW coronal images of the same patient presented in Figure 5 shows a 6-mm hyperintense lesion in the right attic (it was managed with TEA).

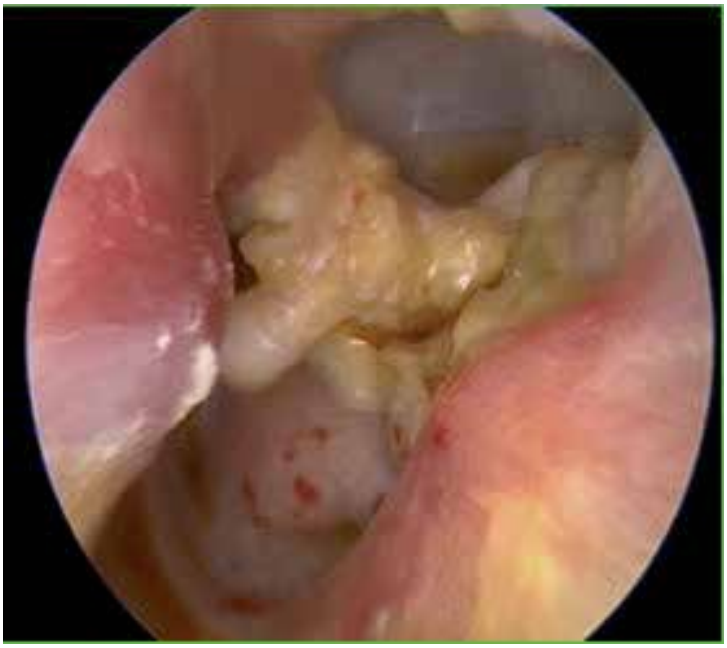

Figure 7. Endoscopic view of left ear recurrent cholesteatoma presented 2.5 years after CWD mastoidectomy.

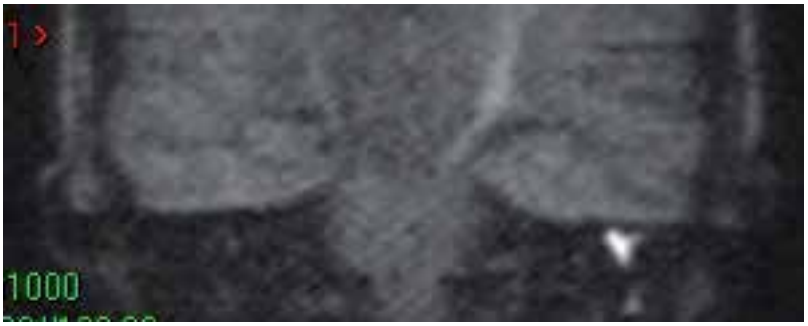

Figure 8. Non-EPI DW coronal images of the same patient presented in Figure 7 shows a 9-mm hyperintense lesion in the left middle ear with an extension to the mastoid (it was managed with TEA).

3. Endoscopic myringoplasty

Recently, different endoscopes have been used in the performance of ear surgery in general and myringoplasty in particular, and the surgical success of endoscope-assisted myringoplasty ranges between 80 and 100 % [40-46]. Myringoplasty can be technically difficult, especially in pediatric patients, due to the narrowness of the external auditory canal and the generally small

http://dx.doi.org/10.5772/60551

size of the ear [46]. Moreover, temporalis fascia grafts and myringoplasties for anterior perforations are more likely to fail in children [40-43,47,48]. Surgical management of anterior perforations requires total exposure of the anterior angle, but a microscope may fail to provide a view of the anterior edge in 73 % of perforations that can, however, be entirely exposed with an endoscope [44]. As a result, drilling of the anterior part of an external auditory canal is usually unavoidable for the repair of anterior perforations when only a microscopic approach is employed [47].

3.1. Surgical technique

Transcanal endoscopic myringoplasties are performed under local or general anesthesia with a chondro-perichondrial graft that is harvested from the tragus and placed medial to the tympanic membrane remnants, utilizing the underlay technique and 14-mm length, 3-mm diameter, 0° and 30° endoscopes (Figures 9 and 10). Tympanomeatal flap is elevated using the 0° endoscope in all the cases, and the 30° endoscope can be utilized for better visualization of anterior perforations. The margins of perforations are freshened using the 0° or 30°endoscopes. A microscope is used for removal of the sclerotic plaques and releasing adhesions surrounding the ossicles when bimanual manipulations are needed.

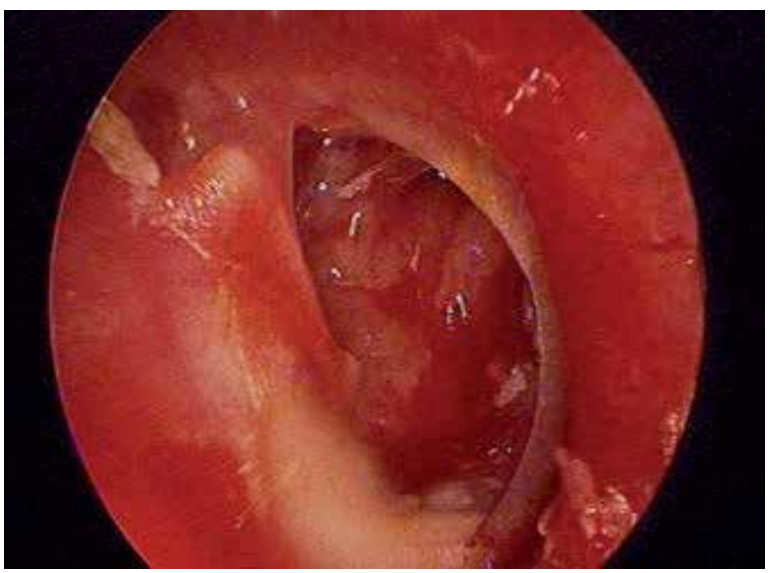

Figure 9. Endoscopic view of a large anterior perforation in the right tympanic membrane.

We found that an endoscope is very effective in ensuring satisfactory approximation of graft material to the perforation margins in small, medium-sized, large and subtotal perforations as well. The transcanal endoscopic myringoplasty had, in our hands, a 100% rate of surgical success for closure of tympanic membrane defects. This technique is especially helpful in patients with narrow external canals, anterior defects and bone overhang, when perforation's

margins are barely, if at all, visible under a microscope. The choice of chondro-perichondrial graft material and the meticulous removal of myringosclerotic plaques can enhance the surgical outcome of endoscopic myringoplasty performed by an experienced otologist.

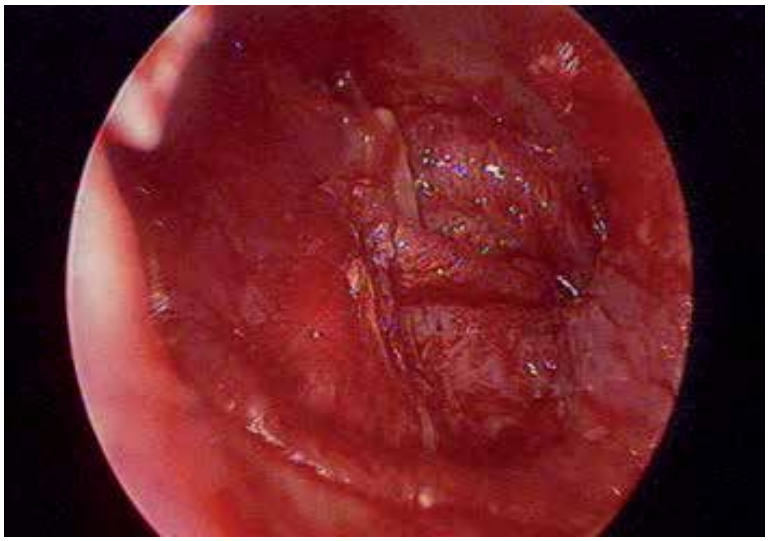

Figure 10. Endoscopic view of the same ear as in Figure 9 at the end of the myringoplasty.

4. Endoscopic stapedotomy

Stapedotomy can be technically difficult and challenging due to anatomic variations in size, configuration, shape or irregularity of the external ear canal. The stapes and oval window niche (OWN) can be obscured by the scutum. Excessive removal of the bone for better visualization of the middle ear (ME) structures can rarely result in subluxation of the incus [49-51]. When the posterior part of the bony annulus is removed to visualize the stapes, the chorda tympani nerve (CTN) can be occasionally touched, stretched, manipulated or transected and result in 20-60% of postoperative taste disorders or tongue symptoms [52-57]. The existing data indicate that the CTN should be preserved whenever possible, especially if surgery is bilateral [53,54,57,58]. Bilateral CTN damage can result in transient or permanent bilateral ageusia of the anterior two-thirds of the tongue, as well as a decreased resting salivary flow rate. In addition, the patients may suffer from transient or persistent, distressing xerostomia or tactile dysguesia [58-60]. However, damage to the CTN and subluxation of the ossicles or stapes fracture significantly decreases in the hands of an experience surgeon.

Endoscopic stapedotomy was introduced in our department with the intent to avoid injury to the CTN when attempting to achieve visibility of the ME structures. The CTN was preserved in all cases, and our preliminary audiometric results were comparable with the others [61-63].

http://dx.doi.org/10.5772/60551

4.1. Surgical technique

The position of the patients is the same as for routine otomicroscopic ear surgeries. The external ear canal is injected with lidocaine 1% with 1:100.000 epinephrine. A fully endoscopic transcanal procedure was undertaken using rigid endoscopes 3 mm diameter, 14-cm length, 0° and 30°. Angled picks and curved scissors and forceps are used in addition to the routine otologic micro-instruments. A posterior tympanomeatal flap is elevated transmeatally with the 0° endoscope and then transposed anteriorly. All the surgeries are performed with a 0° endoscope, while a 30° endoscope can be required to better visualize the OWN, the anterior crus of the stapes, the tympanic portion of the facial nerve and the pyramidal eminence in some cases due to bony overhang in the posterior tympanum. Stapes fixation is confirmed by gentle testing of ossicular chain mobility. The stapes tendon is cut with curved micro-scissors and the stapes is separated from the incus in the incudo-stapedial joint. The anterior and posterior stapedial crus are carefully fractured and the superstructure is removed. The distance between the footplate and medial surface of the long process of the incus was measured to determine the required prosthesis size. The hole in the footplate is created with a Skeeter microdrill using a 0.5-mm diameter diamond burr. A platinum/fluoroplastic piston prosthesis (0.4-mm diameter, 4.5/4.75-mm length) is placed into this hole and fitted along the long process of the incus (Figures 11-14). The appropriate ossicular chain movement with the replaced stapes is ensured by malleus palpation. The tympano-meatal flap is repositioned, and the external auditory canal is filled with Gelfoam® soaked in ear drops containing antibiotics.

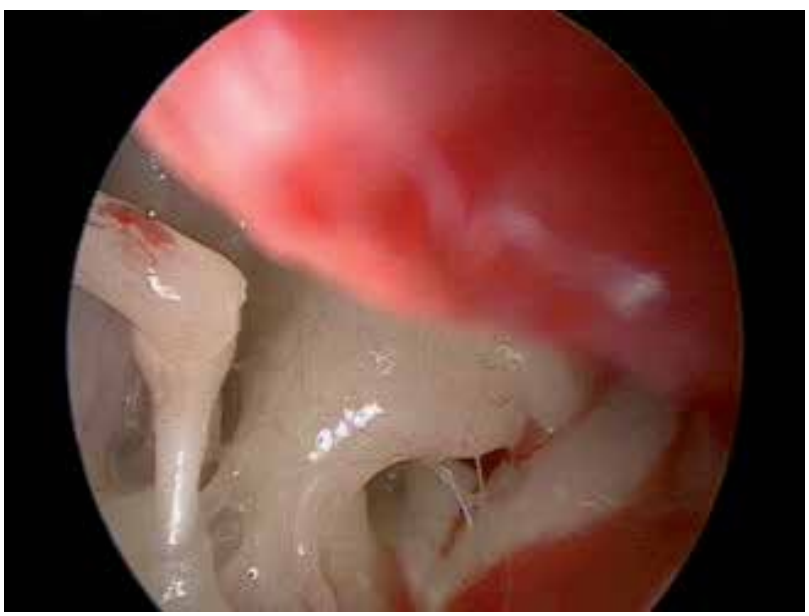

Figure 11. Endoscopic view of the right middle ear after an elevation of the tympano-meatal flap. Good access to the stapes and oval window niche was achieved without removal of the scutum and without touching the chorda tympani nerve.

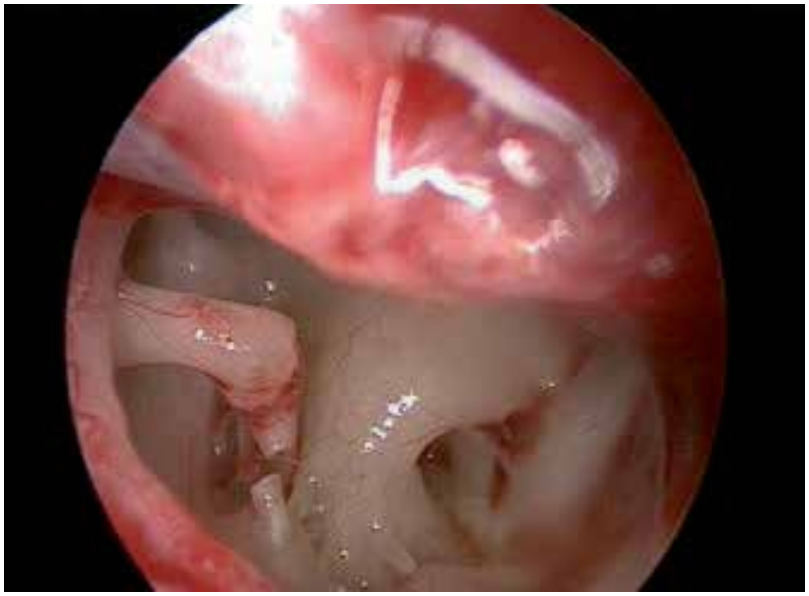

Figure 12. Endoscopic view of the right ear: cutting of the stapedius.

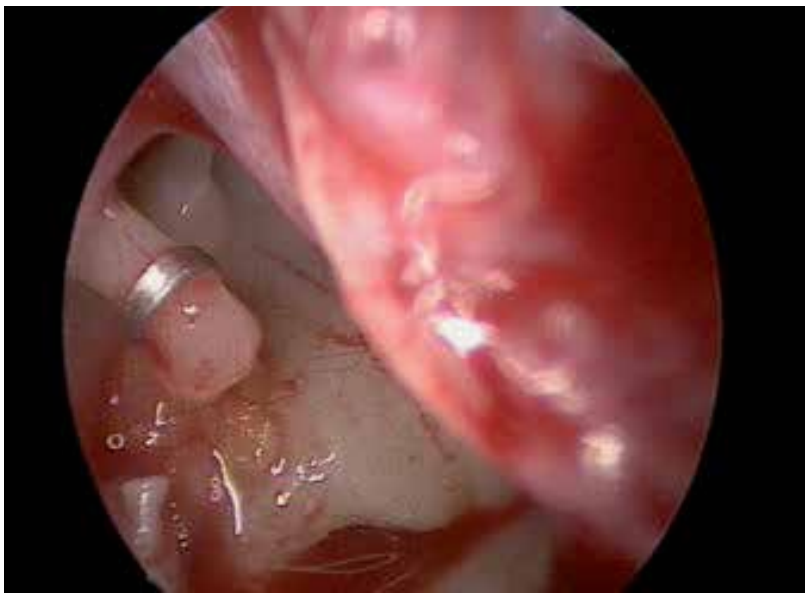

Figure 13. Endoscopic view of piston prosthesis placed in the hole that was created in the footplate and covered with a small piece of fat.

The possible benefits of ES are excellent visibility and accessibility of the stapes and the OWN, and avoiding manipulation of the CTN and blind fracture of the stapedial crurae. Assistance

http://dx.doi.org/10.5772/60551

in using the operating microscope can be required when there is the need for two-hand manipulations for proper placing and coupling of the prosthesis, especially during the surgeon's initial endoscopic procedures. Finally, right-handed surgeon (L.M.) found that the axis of work was initially more comfortable when performing surgery on right ears and that the relative difficulty in creating a hole in the footplate and positioning the prosthesis in left ears could be overcome with more training.

Transcanal fully endoscopic stapedotomy can be utilized in patients with unfavorable external or middle ear anatomy, in candidates for revision or bilateral stapedotomy, in patients with already impaired taste sensation, with food-, smell- or taste-related occupations, and in those for whom the taste of food contributes appreciably to their quality of life.

5. Endoscopic cochlear implantation

Recent developments in cochlear implant electrode array design and modifications of surgical techniques have resulted in improved post-implantation performance by minimizing intra-cochlear damage during implantation [64]. However, electrodes and the surgical procedures used for their insertion still produce intracochlear trauma. An optimal site for cochleostomy in terms of avoiding insertion trauma during cochlear implantation (CI) has not yet been established. Some authors recommend the insertion of the electrode array through the cochleostomy corresponding to the antero-inferior margin of the round window membrane (RWM), while others contend that atraumatic insertion can be achieved directly through the RWM by removing the antero-inferior overhang of the RW niche, drilling down the crista fenestra, and incising the most lateral aspect of the RWM before insertion [64]. Regardless of the site of electrode insertion, the first step is achieving adequate exposure of the RWM in order to facilitate minimally invasive surgery. However, the topographical relationships among the facial nerve (FN), CTN, and RW showed that the widest route of approach through the facial recess (FR) frequently did not point directly towards the RW, but rather towards the basal turn at the promontory [65]. RWM insertion using the FR approach can be more challenging in pediatric patients, with the visibility of the RWM being limited in 11%-22 % of children even after an "optimal" posterior tympanotomy. An extended membranous cochleostomy or conventional bony cochleostomy may be required in some of these cases [66]. Moreover, the access to the RWM may be compromised in an FR approach due to the bony overhangs, abnormal course of the FN, jugular bulb location or abnormalities, anteriorly located sigmoid sinus, narrow FR and an undeveloped mastoid [67-70].

An endoscopic CI involves entering the ME by means of endoscopic transcanal tympanotomy and insertion of the electrode array into the scala tympani via the RW under direct endoscopic control [71,72]. Limited access to the ME structures can result in electrode misplacement, damage to the FN and injury to the CTN when a CI is carried out with an FR approach [73-78]. Indeed, bilateral sacrificing of the CTN due to a narrow FR in bilaterally implanted children can lead to morbidity that has not yet been investigated in depth. One of the reasons for incorrect electrode insertion using the microscopic approach through the FR can be the

presence of a wide subcochlear canaliculus that could be mistaken with the RW niche [72]. Our experience as well as findings of our colleagues showed that the direct visualization of the RWM using a transcanal endoscopic approach permits electrode insertion through the RWM into the scala tympani with less drilling of the niche comparing to the FR technique [72].

5.1. Surgical technique

The procedures are performed with the patients under general anesthesia. The position of the patients, the skin incisions and the drilling of the implant wells are the same as for routine otomicroscopic CI. The external ear canal is injected with lidocaine 1% with 1:100.000 epinephrine. Cortical mastoidectomy until visualization of the incus is performed. A 6 o'clock vertical incision is made in the meatal skin, and a posterior tympano-meatal flap is elevated transmeatally to expose the ME cavity using a rigid 0° endoscope 3 mm in diameter and 14 cm in length held manually, and then transposed anteriorly. The CTN and body of the incus are exposed. Visualization of the incus body serves as a target for drilling and preventing injury to the FN which is located medial to it. The RWM is incised, and the electrodes are passed through the tunnel from the mastoid to epitympanum, medial to the CTN and lateral to the incus into the RW (Figure 15). The tympano-meatal flap is repositioned, and the external auditory canal is filled with Gelfoam® soaked in ear drops containing antibiotics. The surgical procedure can be modified in some procedures as follows: instead of inserting the electrodes through a tunnel that could limit the angle of insertion, an open groove is drilled starting superiorly and laterally to the CTN and ending in the mastoid region. The electrodes are passed through the groove medially to the CTN and laterally to the incus into the scala tympani through the RW, which is then covered with a small piece of temporalis fascia. The groove is filled with bone dust that had been collected during the drilling of the implant well, and covered with a large piece of fascia prior to repositioning of the tympano-meatal flap, aiming to prevent extrusion of the electrode array into the external auditory canal or tracking of the canal skin into the mastoid with cholesteatoma formation. All patients routinely receive intravenous ceftriaxone intra-operatively, followed by a course of oral cephalexin during the first postoperative week.

Fully endoscopic CI with complete electrode insertion via the RW was found more feasible for insertion of Concerto (Medical Electronics, Innsbruck, Austria) electrode followed by HiRes90K (Advanced Bionics Corporation, California, USA) and Nucleus 24 Contour Advance (Cochlear Corporation, Australia) [71].

The main benefits of the TEA to CI are improving the visibility and accessibility of the RWM, obviating the need to divide the CTN in order to obtain adequate exposure of the ME structures, and eliminating the risk of FN injury since the FN is not in the direction of drilling. The open groove technique was used several times in the past by the first author in cases of low-set dura and anteriorly based sigmoid sinus. A follow up of these patients showed that there is no protrusion of the electrode over a period of at least 5 years when the groove is filled with bone dust and is covered with intact skin.

A good knowledge of the endoscopic anatomy of the middle ear and a good practical knowledge of the endoscopic technique are essential to ensure a safe endoscopic CI with good

http://dx.doi.org/10.5772/60551

outcome. An assistance of another surgeon may be required for holding the endoscope during the insertion of the electrode by a right-handed surgeon in the right cochlea and in removal of stylet, when relevant. Moreover, modern electrodes designed for hearing preservation by all companies are very thin and there is the need in bimanual manipulations for their safe and slow insertion requiring the help of an assistant in holding the endoscope. An angle of electrode insertion seems more comfortable in the transcanal approach compared to the epitympanic root of insertion. Right-handed surgeons (e.g. the first author) found that the axis of work was initially more comfortable when performing surgery on left ears and that the relative difficulty in electrode insertion in right ears could be overcome with more training [71]. Complete electrode insertion is achievable into the scala tympani via the round window both in children and adults. This technique can be used as a first surgical option or complementarily to the traditional posterior tympanotomy approach in patients with undeveloped or anomalous mastoid, narrow facial recess, anteriorly based sigmoid sinus, abnormal course of the facial nerve, high jugular bulb, malformed cochlea or distorted anatomy of the middle ear. The main limitation of an endoscopic CI is that it is a difficult one-hand surgery, technically possible only for highly skilled otosurgeons with extensive experience in performing classic aproaches as well as various endoscopic ear procedures. In endoscopic CI, one hand is occupied by the endoscope while the other performs manipulations during endoscopic CI including suctioning, hemostasis and subsequent introduction of the electrode into the cochlea [71]. The lack of stereoscopic vision was not considered to be a drawback by the first author in any surgery.

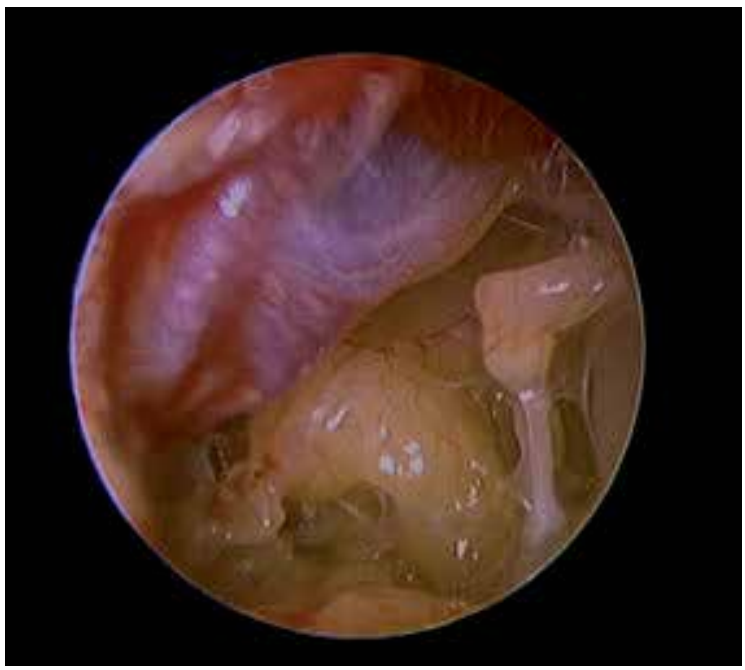

Figure 14. Wide exposure of the middle ear after elevation of the tympano-meatal flap in an endoscopic transcanal cochlear implantation (left ear).

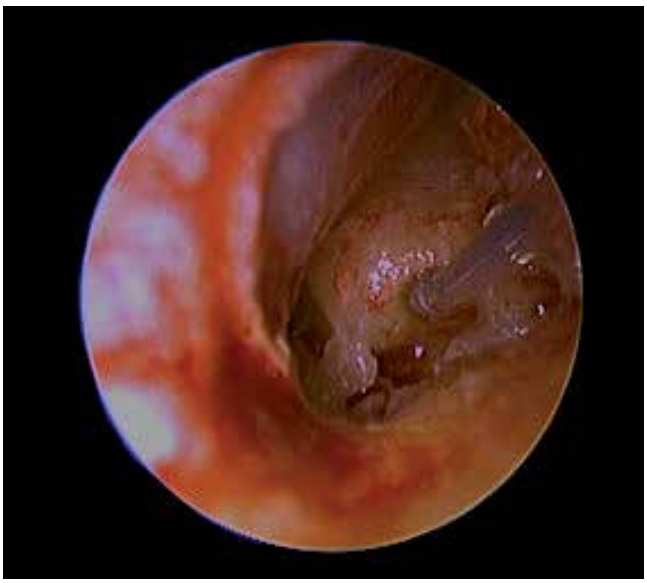

Figure 15. An electrode array passing through the tunnel medial to the chorda tympani nerve and lateral to the incus into the cochlea via the round window in an endoscopic transcanal cochlear implantation (the same ear as in Figure 14).

6. Conclusion

The transcanal endoscopic approach is minimally invasive surgery that can be successfully applied for various ear pathologies. Knowledge on middle ear anatomy, ear radiology and an experience in classic techniques is essential before starting the endoscopic approach. The assistance of an operating microscope may be required when there is the need for two-hand manipulations in dissection of the cholesteatoma from the dehiscent facial nerve, ossicles, stapes footplate, and in some cases of ossicular chain reconstruction, introduction of the electrode array into the cochlea. In inexperienced hands, the endoscopic approach can be associated with complications due to direct trauma from the tip of the endoscope to the facial nerve, the ossicular chain and a low-lying tegmen.

Author details

Lela Migirov* and Michael Wolf

*Address all correspondence to: migirovl@gmail.com

Department of Otolaryngology- Head and Neck Surgery, Sheba Medical Center, affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

http://dx.doi.org/10.5772/60551

References

[1] Thomassin JM, Korchia D, Doris JM. Endoscopic-guided otosurgery in the prevention of residual cholesteatomas. Laryngoscope 1993;103:939-943.

[2] Good GM, Isaacson G. Otoendoscopy for improved pediatric cholesteatoma removal. Ann Otol Rhinol Laryngol 1999;108:893-896.

[3] Badr-El-Dine M. Value of ear endoscopy in cholesteatoma surgery. Otol Neurotol 2002;23:631–635.

[4] El-Meselaty K, Badr-El-Dine M, Mandour M, Mourad M, Darweesh R. Endoscope affects decision making in cholesteatoma surgery. Otolaryngol Head Neck Surg 2003;129:490-496.

[5] Ayache S, Tramier B, Strunski V. Otoendoscopy in cholesteatoma surgery of the middle ear. What benefits can be expected? Otol Neurotol 2008;29:1085-1090.

[6] Migirov L, Shapira Y, Horowitz Z, Wolf M. Exclusive endoscopic ear surgery for acquired cholesteatoma: preliminary results. Otol Neurotol 2011;32:433-436.

[7] Presutti L, Marchioni D, Mattioli F, Villari D, Alicandri Ciufelli M. Endoscopic management of acquired cholesteatoma: our experience. J Otolaryngol 2008;37:481-487.

[8] Bottrill ID, Poe DS. Endoscope-assisted ear surgery. Am J Otol 1995;16:158-163.

[9] Marchioni D, Mattioli F, Alicandri-Ciufelli M, Presutti L. Transcanal endoscopic approach to the sinus tympani: a clinical report. Otol Neurotol 2009;30:758-765.

[10] Tarabichi M. Endoscopic middle ear surgery. Ann Otol Rhinol Laryngol 1999;108:39-46.

[11] Tarabichi M. Endoscopic management of limited attic cholesteatoma. Laryngoscope 2004;114:1157-1162.

[12] Tarabichi M. Transcanal endoscopic management of cholesteatoma. Otol Neurotol 2010;31:580-588.

[13] Tarabichi M. Endoscopic management of acquired cholesteatoma. Am J Otol 1997;18:544-549.

[14] Tarabichi M. Endoscopic management of cholesteatoma: long-term results. Otolaryngol Head Neck Surg 2000;122:874-881.

[15] Wilson KF, Hoggan RN, Shelton C. Tympanoplasty with intact canal wall mastoidectomy for cholesteatoma: long-term surgical outcomes. Otolaryngol Head Neck Surg 2013;149:292-295.

[16] Tomlin J, Chang D, McCutcheon B, Harris J. Surgical technique and recurrence in cholesteatoma: a meta-analysis. Audiol Neurootol 2013;18:135-142.

[17] Stew BT, Fishpool SJ, Clarke JD, Johnson PM. Can early second-look tympanoplasty reduce the rate of conversion to modified radical mastoidectomy? Acta Otolaryngol 2013;133:590-593.

[18] Stankovic M. The learning curve in revision cholesteatoma surgery. Am J Otolaryngol 2013; 34:65-71.

[19] Drahy A, De Barros A, Lerosey Y, Choussy O, Dehesdin D, Marie JP. Acquired cholesteatoma in children: strategies and medium-term results. Eur Ann Otorhinolaryngol Head Neck Dis 2012; 129:225-229.

[20] Gaillardin L, Lescanne E, Morinière S, Cottier JP, Robier A. Residual cholesteatoma: prevalence and location. Follow-up strategy in adults. Eur Ann Otorhinolaryngol Head Neck Dis 2012;129:136-140.

[21] Minovi A, Venjacob J, Volkenstein S, Dornhoffer J, Dazert S. Functional results after cholesteatoma surgery in an adult population using the retrograde mastoidectomy technique. Eur Arch Otorhinolaryngol 2014;271:495-501.

[22] Osborn AJ, Papsin BC, James AL. Clinical indications for canal wall-down mastoidectomy in a pediatric population. Otolaryngol Head Neck Surg 2012;147:316-322.

[23] Vercruysse JP, De Foer B, Somers T, Casselman JW, Offeciers E. Mastoid and epitympanic bony obliteration in pediatric cholesteatoma. Otol Neurotol 2008;29:953-960.

[24] Migirov L, Yakirevitch A, Wolf M. The utility of minimally invasive transcanal endoscopic approach for removal of residual/recurrent cholesteatoma: preliminary results. Eur Arch Otorhinolaryngol. 2014 Nov 21. [Epub ahead of print]

[25] Marchioni D, Mattioli F, Alicandri-Ciufelli M, Presutti L. Transcanal endoscopic approach to the sinus tympani: a clinical report. Otol Neurotol 2009;30:758-765.

[26] James AL. Endoscopic middle ear surgery in children. Otolaryngol Clin North Am 2013; 46:233-244.

[27] De Foer B, Vercruysse JP, Spaepen M, Somers T, Pouillon M, Offeciers E, Casselman JW. Diffusion-weighted magnetic resonance imaging of the temporal bone. Neuroradiology 2010;52:785-807.

[28] Dhepnorrarat RC, Wood B, Rajan GP. Postoperative non-echo-planar diffusion-weighted magnetic resonance imaging changes after cholesteatoma surgery: implications for cholesteatoma screening. Otol Neurotol 2009;30:54-58.

[29] Profant M, Sláviková K, Kabátová Z, Slezák P, Waczulíková I. Predictive validity of MRI in detecting and following cholesteatoma. Eur Arch Otorhinolaryngol 2012;269:757-765.

[30] Edfeldt L, Strömbäck K, Danckwardt-Lilliestrom N, Rask-Andersen H, Abdsaleh S, Wikström J Non-echo planar diffusion-weighted MRI increases follow-up accuracy

after one-step step canal wall-down obliteration surgery for cholesteatoma. Acta Otolaryngol 2013;133:574-583.

[31] Migirov L, Wolf M, Greenberg G, Eyal A. Non-EPI DW MRI in planning the surgical approach to primary and recurrent cholesteatoma. Otol Neurotol 2014;1:121-125.

[32] Brenner DJ, Hall EJ. Computed tomography-an increasing source of radiation exposure. N Engl J Med 2007;357:2277-2284.

[33] Garap JP, Dubey SP. Canal-down mastoidectomy: experience in 81 cases. Otol Neurotol 2001;22:451-456.

[34] De Corso E, Marchese MR, Scarano E, Paludetti G. Aural acquired cholesteatoma in children: surgical findings, recurrence and functional results. Int J Pediatr Otorhinolaringol 2006;70:1269-1273.

[35] Wormald PJ, Nilssen EL. Do the complications of mastoid surgery differ from those of the disease? Clin Otolaryngol Allied Sci 1997;22:355-357.

[36] Wootten CT, Kaylie DM, Warren FM, Jackson CG. Management of brain herniation and cerebrospinal fluid leak in revision chronic ear surgery. Laryngoscope 2005;115:1256-1261.

[37] Dubey SP, Jacob O, Gandhi M. Postmastoidectomy pneumocephalus: case report. Skull Base 2002;12:167-173.

[38] Migirov L, Eyal A, Kronenberg J. Intracranial complications following mastoidectomy. Pediatr Neurosurg 2004;40:226-229.

[39] Moore GF, Nissen AJ, Yonkers AJ. Potential complications of unrecognized cerebrospinal fluid leaks secondary to mastoid surgery. Am J Otol 1984;5:317-323.

[40] Usami S, Iijima N, Fujita S, Takumi Y: Endoscopic-assisted myringoplasty. ORL J Otorhinolaryngol Relat Spec 2001; 63:287-290.

[41] Karhuketo TS, Ilomäki JH, Puhakka HJ: Tympanoscope-assisted myringoplasty. ORL J Otorhinolaryngol Relat Spec 2001;63:353-357; discussion 358.

[42] Konstantinidis I, Malliari H, Tsakiropoulou E, Constantinidis J: Fat myringoplasty outcome analysis with otoendoscopy: who is the suitable patient? Otol Neurotol 2013;34:95-99.

[43] Yadav SP, Aggarwal N, Julaha M, Goel A: Endoscope-assisted myringoplasty. Singapore Med J 2009;50:510-512.

[44] Ayache S: Cartilaginous myringoplasty: the endoscopic transcanal procedure. Eur Arch Otorhinolaryngol 2013;270:853-860.

[45] Raj A, Meher R: Endoscopic transcanal myringoplasty-A study. Indian J Otolaryngol Head Neck Surg 2001;53:47-49.

[46] Mohindra S, Panda NK: Ear surgery without microscope; is it possible. Indian J Otolaryngol Head Neck Surg 2010; 62:138-141.

[47] Halim A, Borgstein J: Pediatric myringoplasty: postaural versus transmeatal approach. Int J Pediatr Otorhinolaryngol 2009;73:1580-1583.

[48] Castro O, Pérez-Carro AM, Ibarra I, Hamdan M, Meléndez JM, Araujo A, Espiña G: Myringoplasties in children: our results. Acta Otorrinolaringol Esp 2013; 64: 87-91. [Article in English, Spanish]

[49] Gołabek W, Szymański M, Siwiec H, Morshed K. Incus subluxation and luxation during stapedectomy. Ann Univ Mariae Curie Sklodowska Med 2003;58:302-305.

[50] Lesinski SG. Causes of conductive hearing loss after stapedectomy or stapedotomy: a prospective study of 279 consecutive surgical revisions. Otol Neurotol 2002; 23:281-288.

[51] Malafronte G, Filosa B. Fisch's reversal steps stapedotomy: when to use it? Otol Neurotol 2009; 30:1128-1130.

[52] Miuchi S, Sakagami M, Tsuzuki K, Noguchi K, Mishiro Y, Katsura H. Taste disturbance after stapes surgery--clinical and experimental study. Acta Otolaryngol Suppl 2009;562:71-78.

[53] Guder E, Böttcher A, Pau HW, Just T. Taste function after stapes surgery. Auris Nasus Larynx 2012;39:562-566.

[54] Clark MP, O'Malley S. Chorda tympani nerve function after middle ear surgery. Otol Neurotol 2007;28:335-340.

[55] Michael P, Raut V. Chorda tympani injury: operative findings and postoperative symptoms. Otolaryngol Head Neck Surg 2007;136:978-981.

[56] Saito T, Manabe Y, Shibamori Y, Yamagishi T, Igawa H, Tokuriki M, et al. Long-term follow-up results of electrogustometry and subjective taste disorder after middle ear surgery. Laryngoscope 2001;111(11 Pt 1):2064-2070.

[57] Yung M, Smith P, Hausler R, Martin C, Offeciers E, Pytel J, et al. International Common Otology Database: taste disturbance after stapes surgery. Otol Neurotol 2008;29:661-665.

[58] Guinand N, Just T, Stow NW, Van HC, Landis BN. Cutting the chorda tympani: not just a matter of taste. J Laryngol Otol 2010;124:999-1002.

[59] Chen JM, Bodmer D, Khetani JD, Lin VV. Tactile dysgeusia: a new clinical observation of middle ear and skull base surgery. Laryngoscope 2008; 118:99-103.

[60] Mandel L. Hyposalivation after undergoing stapedectomy. J Am Dent Assoc 2012;143:39-42.

[61] Migirov L, Wolf M. Endoscopic transcanal stapedotomy: how I do it. Eur Arch Otorhinolaryngol. 2013;270:1547-1549.

[62] Poe DS. Laser-assisted endoscopic stapedectomy: a prospective study. Laryngoscope 2000;110 (5 Pt 2 Suppl 95):1-37.

[63] Nogueira Júnior JF, Martins MJ, Aguiar CV, Pinheiro AI. Fully endoscopic stapes surgery (stapedotomy): technique and preliminary results. Braz J Otorhinolaryngol 2011;77:721-727 [Article in English, Portuguese].

[64] Skarzynski H, Lorens A, Matusiak M, Porowski M, Skarzynski PH, James CJ. Partial deafness treatment with the nucleus straight research array cochlear implant. Audiol Neurootol 2012;17:82-91.

[65] Hamamoto M, Murakami G, Kataura A. Topographical relationships among the facial nerve, chorda tympani nerve and round window with special reference to the approach route for cochlear implant surgery. Clin Anat 2000;13:251-256.

[66] Leong AC, Jiang D, Agger A, Fitzgerald-O'Connor A. Evaluation of round window accessibility to cochlear implant insertion. Eur Arch Otorhinolaryngol 2013;270:1237-1242.

[67] Song JJ, Park JH, Jang JH, Lee JH, Oh SH, Chang SO, Kim CS. Facial nerve aberrations encountered during cochlear implantation. Acta Otolaryngol 2012;132:788-794.

[68] Leung R, Briggs RJ. Indications for and outcomes of mastoid obliteration in cochlear implantation. Otol Neurotol 2007;28:330-334.

[69] Kuhn MA, Friedmann DR, Winata LS, Eubig J, Pramanik BK, Kveton J, Kohan D, Merchant SN, Lalwani AK. Large jugular bulb abnormalities involving the middle ear. Otol Neurotol 2012;33:1201-1206.

[70] Jang JH, Song JJ, Yoo JC, Lee JH, Oh SH, Chang SO. An alternative procedure for cochlear implantation: transcanal approach. Acta Otolaryngol 2012;132:845-849.

[71] Migirov L, Shapira Y, Wolf M. The feasibility of endoscopic transcanal approach for insertion of various cochlear electrodes: a pilot study. Eur Arch Otorhinolaryngol. 2014 Mar 12. [Epub ahead of print]

[72] Marchioni D, Grammatica A, Alicandri-Ciufelli M, Genovese E, Presutti L. Endoscopic cochlear implant procedure. Eur Arch Otorhinolaryngol 2014;271:959-966.

[73] Orús Dotú C, Venegas Pizarro Mdel P, De Juan Beltrán J, De Juan Delago M. [Cochlear reimplantation in the same ear: findings, peculiarities of the surgical technique and complications]. Acta Otorrinolaringol Esp 2010;61:106-117. [Article in Spanish]

[74] Mouzali A, Ouennoughi K, Haraoubia MS, Zemirli O, Triglia JM. Cochlear implant electrode array misplaced in Hyrtl's fissure. Int J Pediatr Otorhinolaryngol 2011;75:1459-1462.

[75] Nevoux J, Loundon N, Leboulanger N, Roger G, Ducou Le Pointe H, Garabédian EN. Cochlear implant in the carotid canal. Case report and literature review. Int J Pediatr Otorhinolaryngol 2010;74:701-703.

[76] Hara M, Takahashi H, Kanda Y. The usefulness of reconstructed 3D images in surgical planning for cochlear implantation in a malformed ear with an abnormal course of the facial nerve. Clin Exp Otorhinolaryngol 2012;5 Suppl 1:S48-52.

[77] Wagner JH, Basta D, Wagner F, Seidl RO, Ernst A, Todt I. Vestibular and taste disorders after bilateral cochlear implantation. Eur Arch Otorhinolaryngol 2010;267:1849-1854.

[78] Brito R, Monteiro TA, Leal AF, Tsuji RK, Pinna MH, Bento RF. Surgical complications in 550 consecutive cochlear implantation. Braz J Otorhinolaryngol 2012;78:80-85. [Article in English, Portuguese]

Chapter 12

Endoscopy for Skull Base Surgery

Boonsam Roongpuvapaht,
Kangsadarn Tanjararak and Ake Hansasuta

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60556

Abstract

The endonasal approaches for skull base surgery have evolved in the recent decade. There are many publications of this technical safety and good outcomes, comparable with conventional procedure and have less morbidities. In this chapter, the authors describe the approach and surgical technique for each area of the skull base.

Keywords: Endoscopy, Skull base

1. Introduction

Lesions of paranasal sinuses, as well as those within skull base region, have long been challenging to rhinologists and neurosurgeons for several decades. Historically, the only available surgical approaches for these pathologies have traditionally been extensive and, often, invasive open procedures. Despite ample corridor created by open surgery, its major drawbacks during the surgery have been the poor visualization due to suboptimal illumination and magnification of the surgical fields. This fact could become more significant in those with pathologies in deep, narrow or complex anatomical areas. In some cases, en bloc tumor resection can be more easily performed through an open technique while in deep and difficult lesion may not possible to obtain the precise and free surgical margin due to poor visualization. In addition to the limited visualization by open surgery, these massive maneuvers can result in significant blood loss, morbidity or mortality.

Based on important principles, any evolution of surgical equipment and techniques has the same crucial concepts. First, it needs to minimize the associated surgical morbidity/mortality.

Second, it should maintain the patients' functional outcomes, parallel to the high success rate of surgery, i.e., for neoplasms, to achieve oncological control.

Later, development of surgical technique utilizing microscopy has been applied to the operative management of intracranial pathologies. Microsurgery had proven better patients' outcome compared to the historic open procedures, likely from the improved visualization and magnification of the operative field. Consequently, smaller skin incision and less amount of bone removal can achieve similar, if not better, overall result of the same lesions. Patients' safety as well as satisfaction has been greater with microscopic surgery. Therefore, microsurgery has been recognized as the standard of care for many neurosurgical and otolaryngological procedures. However, despite the vast usefulness of the microscope in neurosurgery and otolaryngology, it is not perfect. For the fact, shadow from an outside light source, an operating microscope, can hinder clear visualization at corners of the lesions or critical structures. This drawback is very obvious if one performs an operation through a small and narrow passage, i.e., transsphenoidal route either by sublabial or transnasal technique. This may, indeed, result in a subtotal resection.

For the past few decades, innovation of endoscopy has been developed and accepted as a minimally invasive technique. Various endoscopic tools and techniques have been applied to appropriate organs in different surgical fields. Unlike an outside light source from an operating microscope as mentioned above, visualization under endoscope has the superiority, obtaining a panoramic view with minimal or no shadow due to its light coming off the end of an endoscope. This is very factual through the narrow corridor, i.e., transsphenoidal route. In addition, endoscope provides excellent magnification that enhances the critical anatomical view beyond the operating site. Furthermore, the variety of angled lens endoscope allows surgeons to inspect "hidden" areas, especially "around the corners." Hence, some surgeons have been utilizing endoscopy as an assisting tool along with open or microsurgery so that it enhances visualization around the corners to improve resection of the target pathology. It reassures the complete removal of the tumors.

The treatment of the sinonasal tumors by endoscopy has been widely employed after the evolution of the endoscopic application for the paranasal and sinus diseases in the 1980s, which was introduced by Wigand and Messerklinger.[1, 2] Subsequently, the more properly designed endonasal instruments were developed and adapted to the endoscopic methods. This was popularized and spread over the otolaryngologists world by Stammberger and Kennedy.[3, 6] The endoscopic surgery for the intracranial pathology was first described in 1920s. Then, it was mainly applied within the ventricular system for the treatment of hydrocephalus. In 1990s it was, for the first time, reported for the treatment of pituitary lesions via transsphenoidal route as a collaboration between the otolaringologists and the neurosurgeons.[7, 11]

Recently, endoscopy has been employed for surgical treatment of various sinonasal pathologies. With the success of endoscopic sinus surgery, this approach has progressed further to the treatment of intracranial lesions namely in the vicinity of the skull base. In the aspect of skull base area, by accessing the cranial base via the natural anatomical corridors such as the nostrils or the oral cavity, endoscopic procedures can preserve critical and normal structures without leaving patients with cutaneous/visible scar. Moreover, better visualization with little, or no, brain retraction can be obtained. Hence, improvement of oncological control along with

http://dx.doi.org/10.5772/60556

minimal functional morbidities has been reported by many authors. To date, there have been several publications that reiterated excellent results of the surgical outcomes to prove the efficacy of this innovative technique. Therefore, in some pathology, endoscopic procedures are considered one of the available standard treatments.

The endoscopic surgery has been expanded for the treatment of the lesions along the skull base, including both the median sagittal and paramedian coronal planes in the fashion of the multidisciplinary team approach.[12, 14] True team work can enhance the most benefit of the surgical techniques. The maintaining of clear visualization simultaneous with the two-hand dissecting technique cannot be accomplished independently. Moreover, the team approach has more efficient potential to manage the inevitable crisis during surgery.

Parallel to the surgical technique advancement, the safety from the new surgical method should be assessed for clinical use. Although, the endoscopic surgery has been known as a minimally invasive technique, it also carries a risk of complications. The incidence of complication has the different degrees of possibility depending on the surgical pathologies and procedures. The death and neurological deficits (transient or permanent) are the definite sequelae of the major complications from the endoscopic skull base surgery that includes the cerebrospinal fluid (CSF) leak, the intracranial infection and the neurovascular injury. The following rhinological symptoms have been considered as the minor complications as they don't cause severe morbidities for the patients: the nasal obstruction, the change of smell and sinusitis.

2. Patient selection

Not all the diseases could manage with endonasal technique. If the disease involves subcutaneous of skin or skin itself, the external approach should be more proper. If the tumor extends lateral to the center of the orbit, the orbit itself will be in the axis of the surgical corridor and block the working space. However, the patient selection depends on surgeon's experience.

3. Instrument

Author recommends using a high-definition camera, 4-mm telescopes in various angles (0, 30, 45, 70 degree), a powered instrument (microdebrider, ultrasonic aspirator, drill), hemostatic materials and devices and material for skull base reconstruction. The image-guided surgery system is highly recommended.

4. Surgical approaches

Surgical approaches for endonasal skull base can be classified into two groups based on anatomical view: sagittal plane (Figure 1) and coronal plane (Table 1).

Sagittal plane	Coronal view
Transfrontal Transcribiform Transplanum Transellar Transclival Transodontoid	Anterior cranial fossa -Orbital approach Middle cranial fossa -Pterygomaxillary fossa -Infratemporal fossa Posterior cranial fossa -Parapharyngeal space

Table 1. Surgical approaches

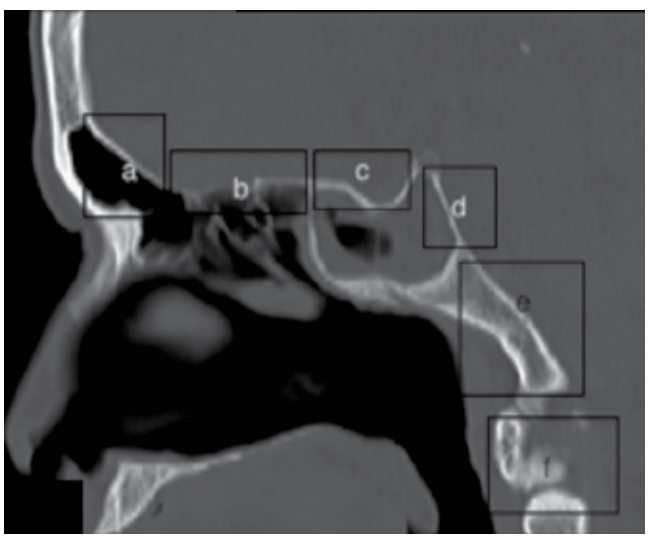

Figure 1. Endonasal approaches to the skull base in sagittal view. a) Transfrontal b) Transcribiform c) Transplanum d) Transsellar e) Transclival f) Transodontoid

4.1. Sagittal view

4.1.1. Transfrontal approach

This approach can be used in chronic frontal sinusitis, frontal fibro-osseous lesion and frontal sinus mucocele. This area can be reached by Draf III procedure or modified Lothrop which has to remove posterior part of nasal septum, remove the bone anterior to frontal sinus and connect both frontal sinus together by removing interfrontal sinus septum (Figures 3 and 4).

http://dx.doi.org/10.5772/60556

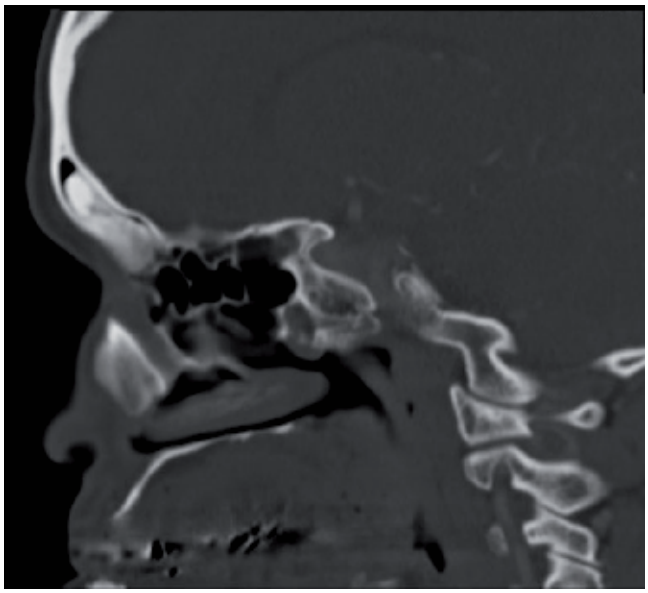

Figure 2. Sagittal view of CT scan shows osteoma in frontal sinus.

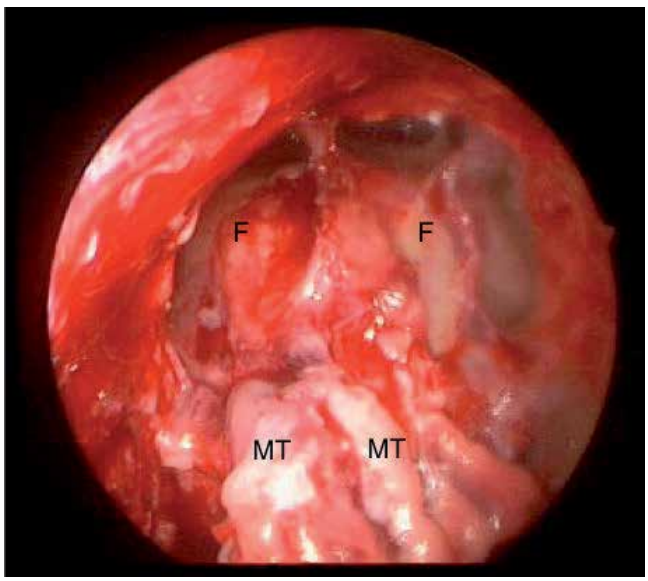

Figure 3. Endonasal view of both frontal sinus after Draf III procedure; F, frontal sinus; MT, middle turbinate.

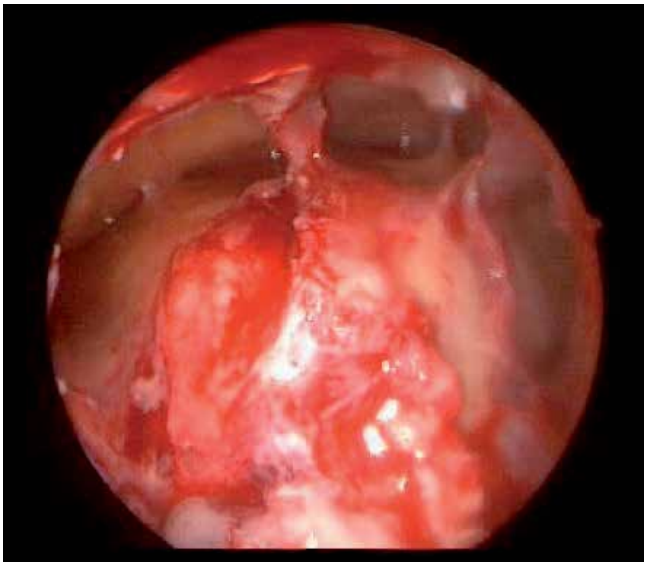

Figure 4. Endonasal view of both frontal sinus after Draf III procedure; F, frontal sinus; MT, middle turbinate.

4.1.2. Transcribiform approach

This approach is commonly utilized for olfactory area tumor such as olfactory neuroblastoma (esthesioneuroblastoma) and olfactory groove meningioma. This approach starts with complete sphenoethmoidectomy and Draf IIa/b or Draf III. The nasal septum removal should start from the crista galli to the sphenoid sinus.The anterior ethmoidal artery and posterior ethmoidal artery should be cauterized and transected to prevent bleeding and decrease the blood supply to the tumor. Cribiform plate should be thinned with diamond burr prior to its removal by bone rongeur so that the dura is clearly seen. The required area of bone exposure usually depends on oncological margin. The maximal bone removal at the cribiform plate can be from posterior wall of frontal sinus to planum sphenoidale in sagittal view and from medial wall of orbit to the other one in coronal view. The crista galli is thinned and removed from from its dural attachment, the falx cerebri. After dural opening, similar microsurgical technique for tumor dissection is employed by two-hand method.

4.1.3. Transplanum approach

Neoplasms at suprasellar area, such as tuberculum meningioma (Figure 9) or craniopharyngioma, typically require this particular approach. Bone removal at the posterior nasal septum and bilateral sphenoidotomy must be done as well as identification of optic nerves and opticocarotid recesses on both sides. Using similar steps as previously mentioned, the bone of skull base should be thinned and removed (Figures 10, 11). After dural opening, awareness of and early identification of critical structures, i.e., optic nerves and chiasm, internal carotid and anterior cerebral arteries and pituitary gland and its stalk (Figures 12, 13, 14), are critically

http://dx.doi.org/10.5772/60556

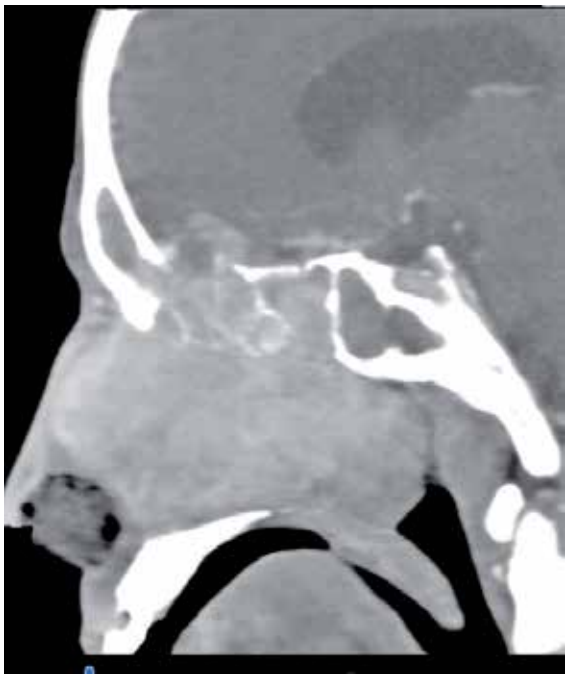

Figure 5. CT of an olfactory neuroblastoma. The tumor fully occupies the sino-nasal cavity and destroys the cribiform plate with intracranial extension.

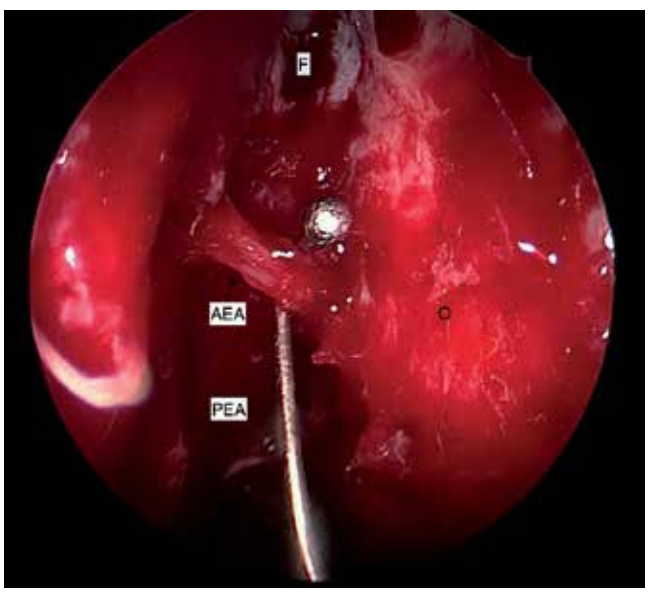

Figure 6. Left endonasal view, after endoscopic sinus surgery. The anterior ethmoidal artery was pulled with sinus seeker. F: frontal sinus O: orbit AEA: anterior ethmoidal artery PEA posterior ethmoidal artery

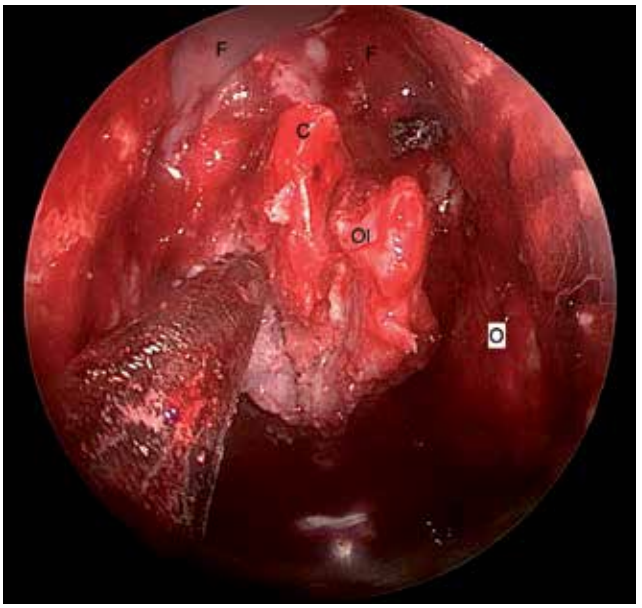

Figure 7. Endoscopic view of Draft III procedure and removal of nasal septum. The crista galli (C) in midline and first branch of olfactory nerve lateral to crista galli both sides are shown. F: frontal sinus C: crista galli Ol: first branch of olfactory nerve O: orbit

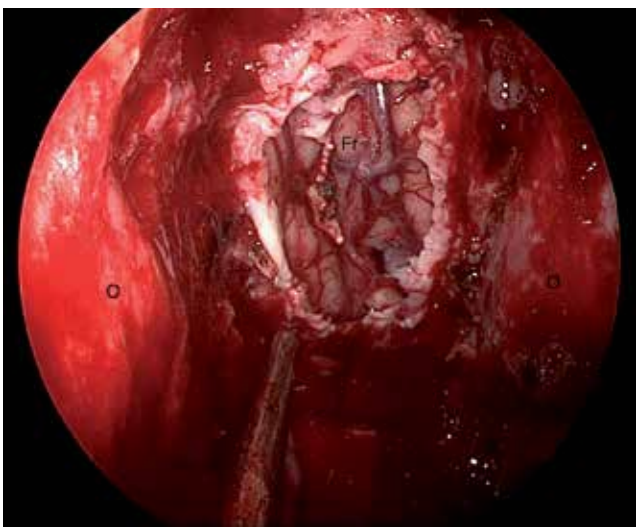

Figure 8. Endoscopic view after removing cribiform plate and dural opening demonstrates frontal lobe and orbit on both sides. O: orbit Fr: frontal lobe

important. Bi-manual technique, using similar microsurgical dissection, should be delicately performed. In some craniopharyngiomas, entry to the third ventricle is necessary for further tumor resection (Figures 15, 16).

http://dx.doi.org/10.5772/60556

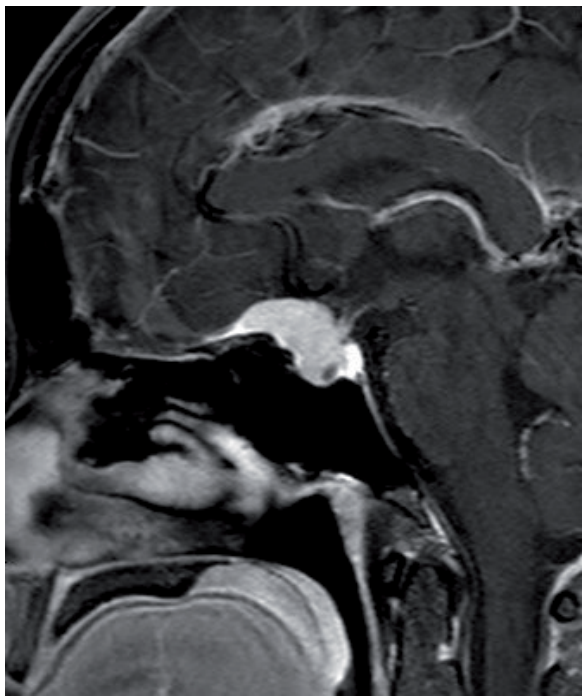

Figure 9. Sagittal MRI shows planum meningioma with compression of optic apparatus. The anterior cerebral artery complex is superior to the tumor.

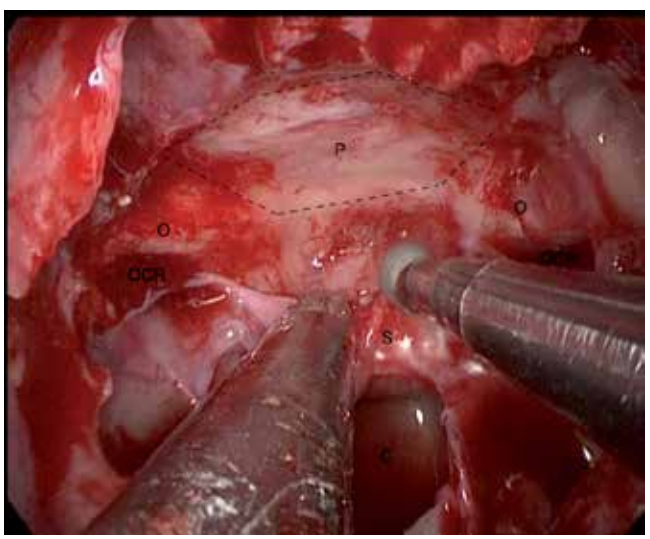

Figure 10. Endonasal view of planum sphenoidale and sella. P: planum sphenoidale (bony area within dashed line needs to be removed) O: optic nerve OCR: optico-carotid recess S: sellar C: clivus

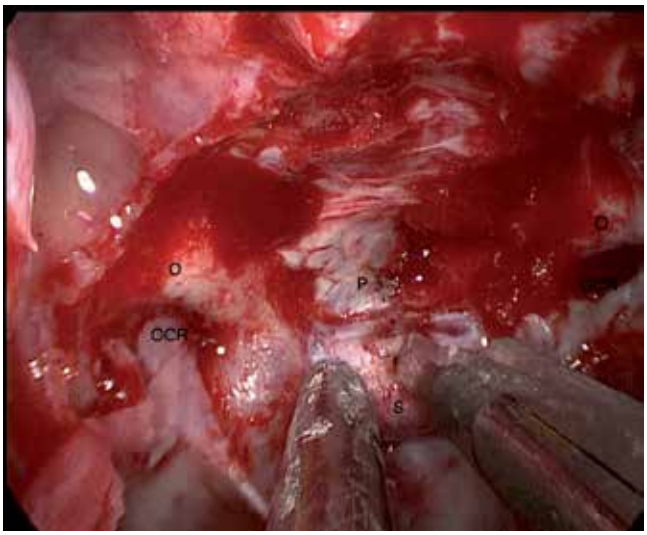

Figure 11. Endoscopic view demonstrates incision of the dura after removal of bony part of skull base. O: optic nerve OCR: optico-carotid recess P: planum sphenoidale S: sellar

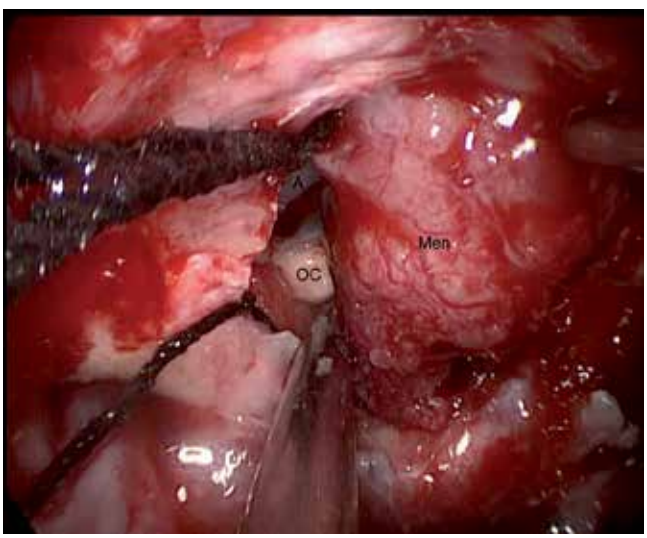

Figure 12. Endoscopic view after partial tumor removal illustrates the meningioma(Men), showing optic chiasm(OC) and anterior cerebral artery(A). Men: meningioma OC: optic chiasm A: anterior cerebral artery (A1 segment)

http://dx.doi.org/10.5772/60556

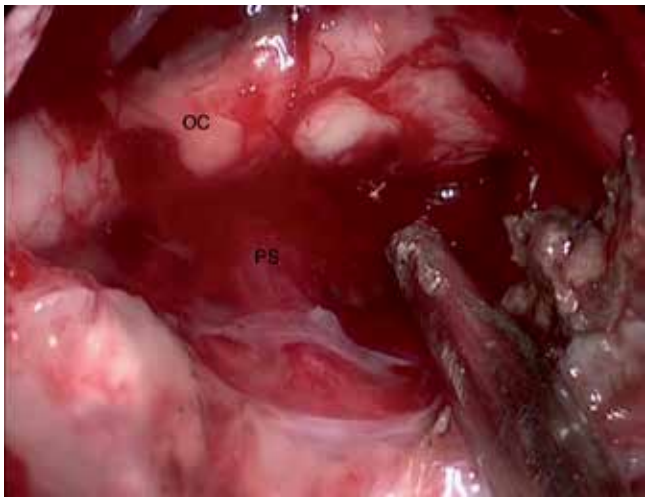

Figure 13. Endoscopic view after complete tumor removal depicts optic chiasm and pituitary stalk. OC: optic chiasm PS: pituitary stalk

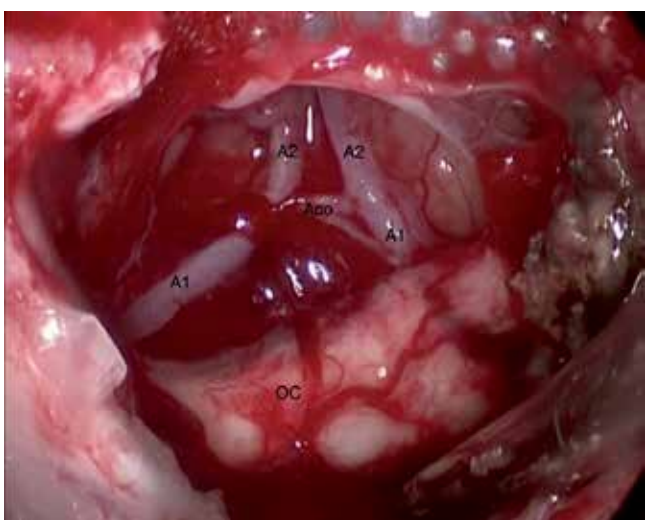

Figure 14. Endoscopic view of 30 degree angle lens, after complete tumor removal, shows more superiorly located structure. OC: optic chiasm A1: left and right anterior cerebral artery (A1 segment) Aco: Anterior communicating artery A2: left and right anterior cerebral artery (A2 segment)

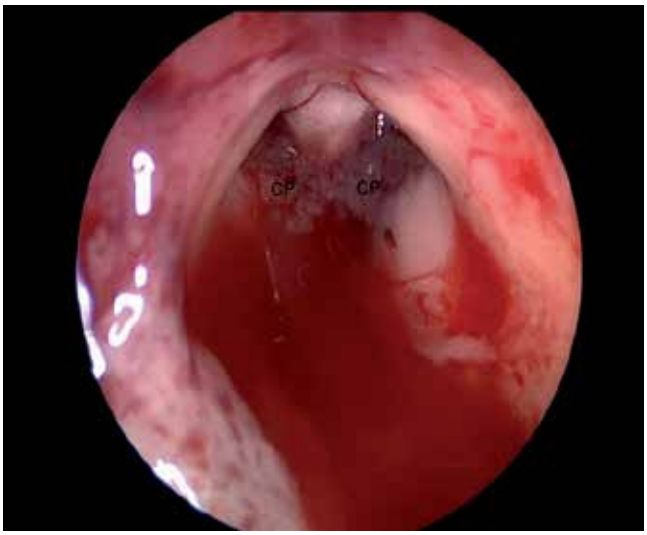

Figure 15. Endoscopic view using 30 degree lens looking upward after removal of craniopharyngioma depictsboth foramen of Monroe. CP: choroid plexus running from both lateral ventricle into the third ventricle

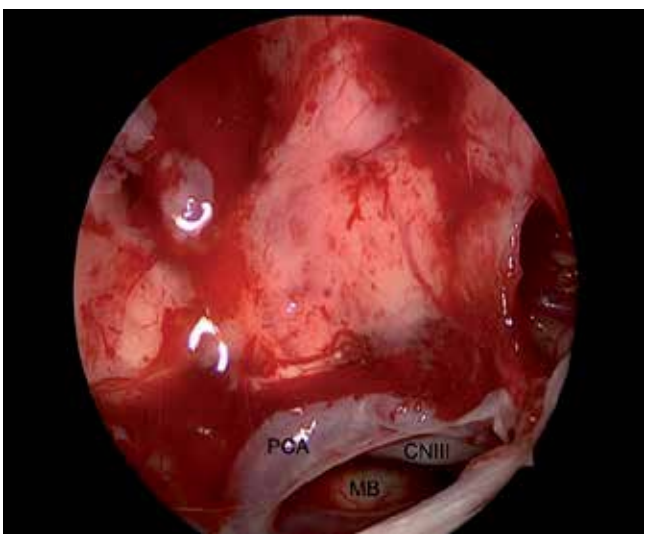

Figure 16. Endoscopic view using 30 degree lens looking downward after removal of craniopharyngioma reveals posterior structures. PCA: posterior cerebral artery CNIII: oculomotor nerve MB: mammillary bod

http://dx.doi.org/10.5772/60556

4.1.4. Transsellar approach

The most common disease for this approach is pituitary adenoma. This is the basic procedure of skull base that a surgeon should start to practice. After posterior nasal septectomy and bilateral sphenoidotomy, the sellar will come into the center of view. All the landmarks structures, e.g., internal carotid artery (ICA), optic nerve, optico-carotid recess, sellar, clivus and planum sphenoidale, should be identified. Sellar bone can be removed with diamond bur and manual instrument to expose the dura. The dura needs to be opened by using bipolar diathermy for hemostasis prior to incision with knife. The pituitary adenoma could be removed in a variety of techniques depending on the consistency of the tumor. The pituitary stalk, superior hypophyseal should be taken care for prevention of long-term endocrine malfunction.

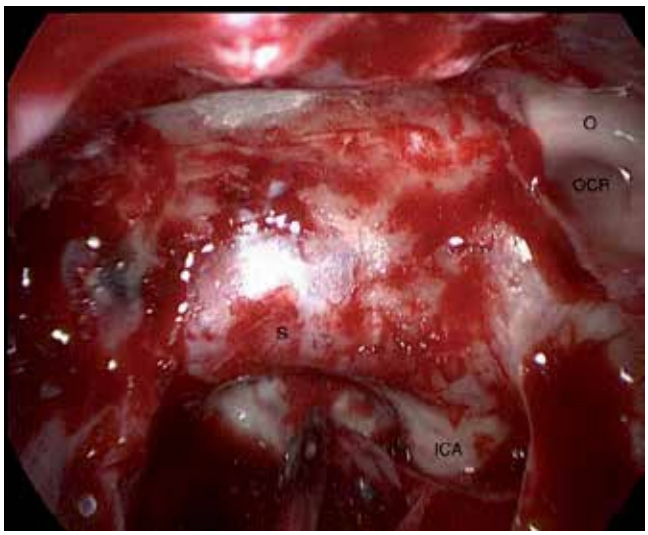

Figure 17. After removal of sellar bone, the sellar dura is exposed. O: optic nerve OCR: optico-carotid recess S: sellar ICA: internal carotid artery

4.1.5. Transclival approach

The clivus extends from sphenoid floor to foramen magnum. The common disease in this area includes meningioma and chordoma. This approach provides direct access to anterior surface of brainstem. The bony part of the clivus has a rich blood supply which surgeon should be cautious. After bony removal with diamond drill, the dura should carefully be incised because the 6th cranial nerve could be injured as it runs more superficially laterally. The vertebrobasillar artery should be carefully dissected and preserved.

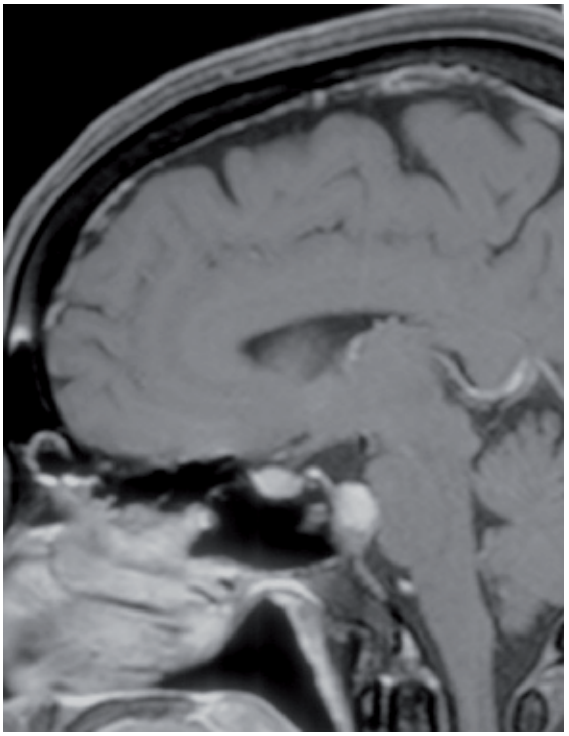

Figure 18. Sagittal MRI shows clivus chordoma pushing on brainstem, patient visit with diplopia from left lateral rectus muscle palsy.

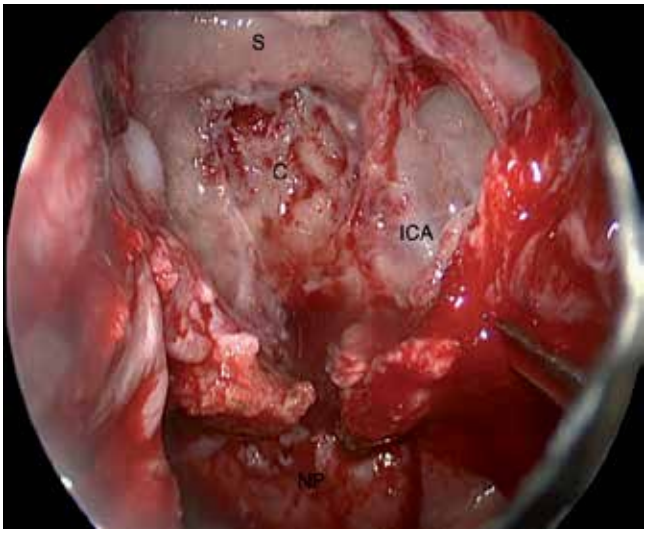

Figure 19. Endonasal view while drilling clivus. S: sellar C: clivus ICA: internal carotid artery NP: nasopharynx

http://dx.doi.org/10.5772/60556

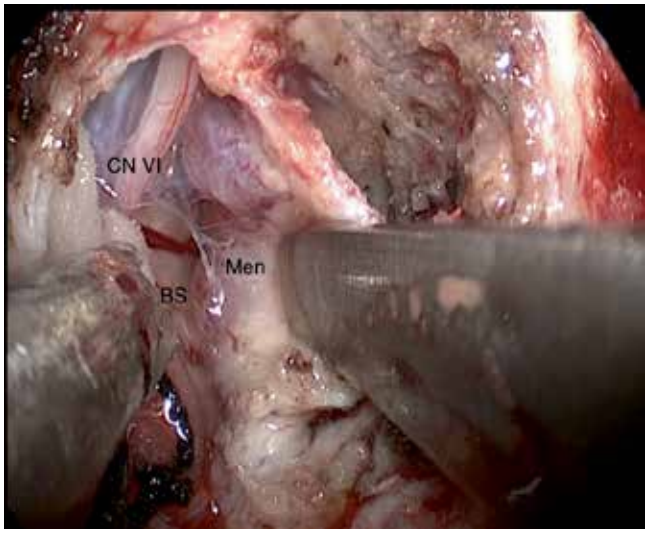

Figure 20. Endoscopic view after removal of bony clivus and incision of dura; meningioma was partially removed and retracted laterally. CN VI: abducens nerve Men: meningioma BS: brainstem

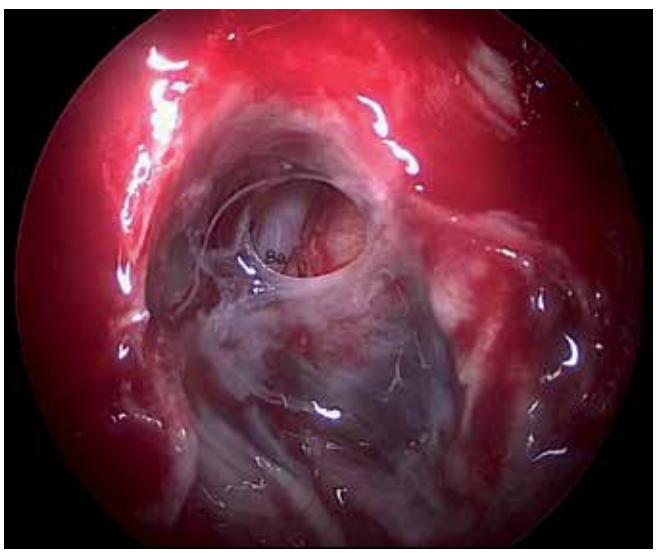

Figure 21. Endoscopic view after complete removal of tumor depicts the basilar artery lies posterior to arachnoid membrane, running vertically in front of the brainstem. Ba: basilar artery

4.1.6. Transodontoid approach

This approach allows access to foramen magnum and upper cervical spine (C1 and C2). Common diseases are pannus formation in rheumatoid arthritis and foramen magnum

meningioma. This procedure is identical with transclival approach but necessitates further inferior dissection of nasopharyngeal mucosa and muscular structures. Again, the bone of anterior C1 and C2 should be thinned with high-speed drill before its removal.

4.2. Coronal view

4.2.1. Orbital approach

This approach use for tumor involve orbit, orbital roof. Start with complete endoscopic sinus surgery (middle maxillary antrostomy, complete sphenoethmoidectomy, frontal sinusotomy) and make a wide sinus cavity to ensure the orbital fat after decompression will not occlude to sinonasal drainage pathway. The lamina papyracea is elevated from periorbita like peeling an egg shell. The periorbita can be resected with sharp instrument. If the tumor is intraconal, the surgical corridor should be done between medial and inferior rectus muscle while having medial rectus retraction externally.

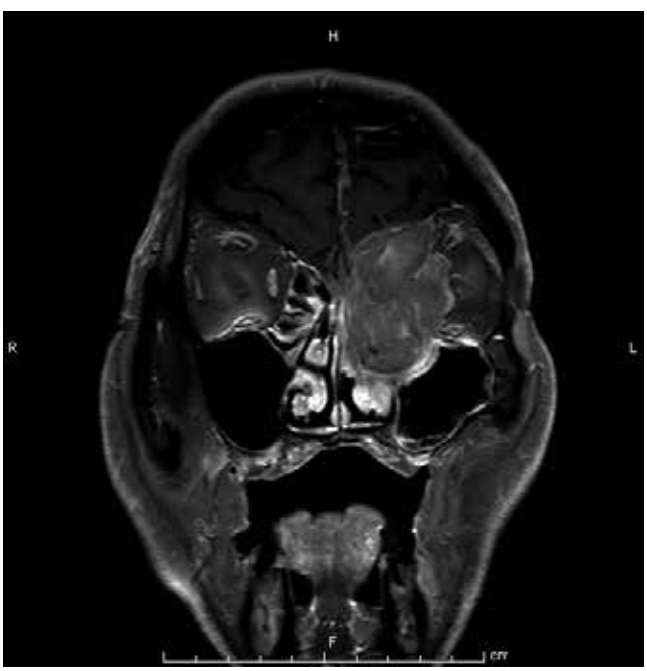

Figure 22. MRI shows tumor in left ethmoid sinus invading the left orbit.

http://dx.doi.org/10.5772/60556

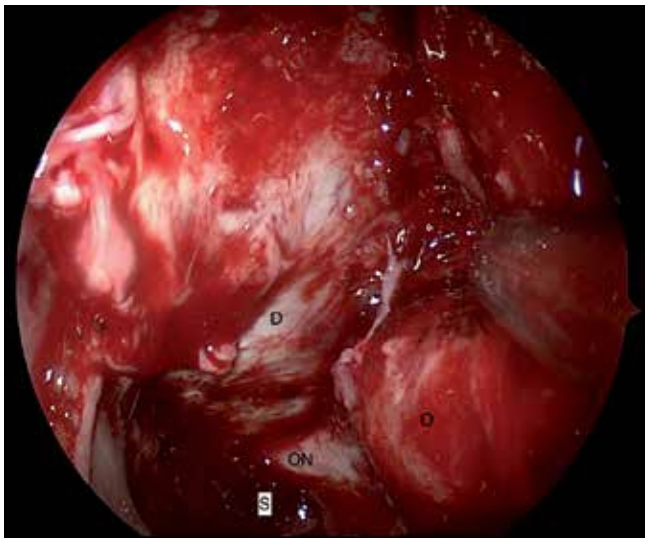

Figure 23. Endoscopic view after removal of the tumor, left cribiform plate, lamina papyracea and decompression of left optic nerve. The medial wall of orbit still bulging from the residual intraconal tumor. O: orbit D: dura ON: optic nerve S: sphenoid sinus (left)

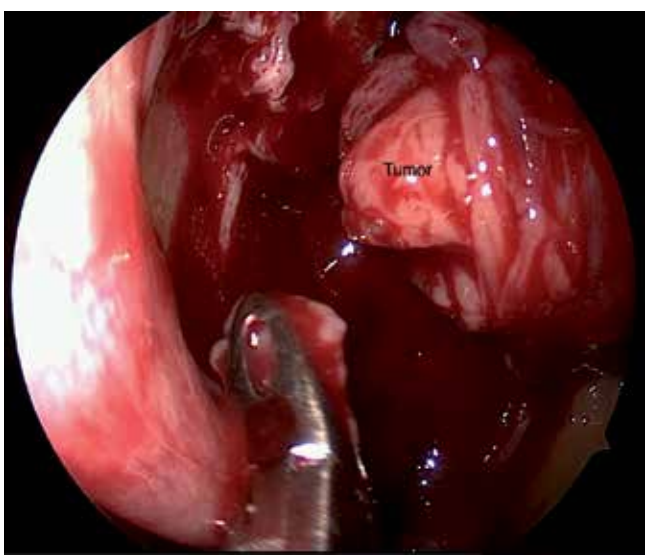

Figure 24. After incision of the periorbita, eye ball was gently compressed by assistant surgeon; the tumor will show up into the surgical field. The tumor could be removed by pushing externally and by intranasal dissection.

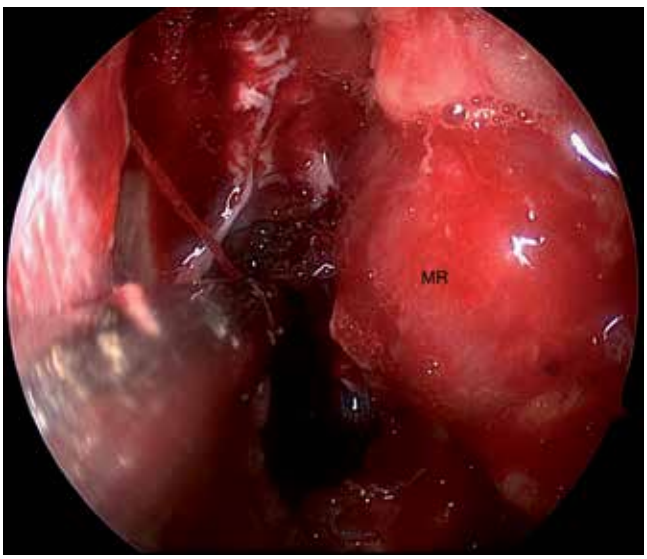

Figure 25. After total removal of the tumor, the medial rectus muscle can be clearly seen. The medial rectus muscle is retracted downward and upward for inspection with angle telescope to confirm that no tumor was left behind. MR: medial rectus muscle

4.2.2. Transpterygoid approach

This approach is utilized for access to middle cranial fossa. By removing the pterygoid bone, it can be used as a margin for tumor in sinus area, e.g., nasopharyngeal carcinoma. Other pathologies require access to the lateral recess of sphenoid such as meningoencephalocele and dural defect repair. This approach starts with maxillary antrostomy (medial maxillectomy is necessary if dissection has to be done at the lower level of inferior turbinate) and complete sphenoethmoidectomy. The sphenopalatine artery, which runs just behind ethmoidal process of palatine bone, should be cauterized or ligated (Figure 26). High-speed drill is typically necessary for removing medial and lateral pterygoid plate. The medial and lateral pterygoid muscles lie beneath the bone plate where there is rich vascular supply; hence, careful hemostasis should be employed prior to performing deeper dissection (Figure 27).

4.2.3. Infratemporal fossa approach

The location of infratemporal space is lateral to the lateral pterygoid plate. This space contains fat, internal maxillary artery, CN V2 (infraorbital nerve) and CN V3(mandibular nerve). The internal maxillary artery should be controlled with vascular clip or electrocautery. Infraorbital nerve is typically identified at the roof of posterior wall of maxillary sinus. For the mandibular nerve, it usually runs laterally to the lateral pterygoid muscle.

http://dx.doi.org/10.5772/60556

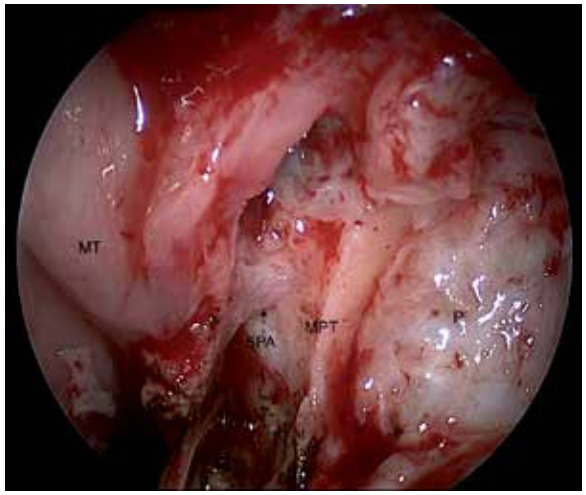

Figure 26. Endoscopic view of left nasal cavity after endoscopic sinus surgery and medial maxillectomy showing sphenopalatine artery running horizontally. MT: middle turbinate SPA: sphenopalatine artery MPT: medial pterygoid plate P: posterior wall of maxillary sinus

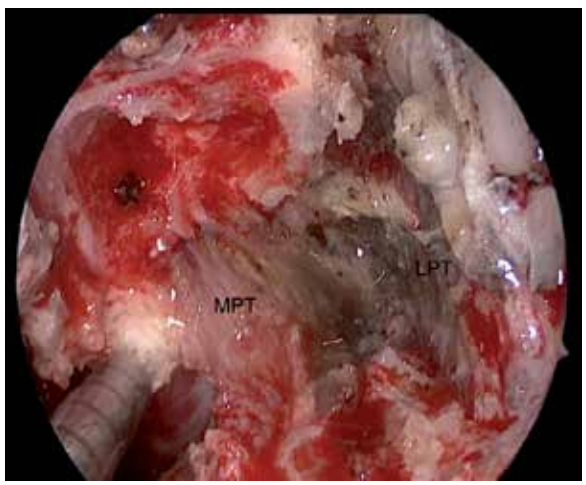

Figure 27. Endoscopic view after sphenopalatine artery is cauterized along with removal of pterygoid plate; the medial pterygoid and lateral pterygoid muscles can be identified. MPT: medial pterygoid muscle LPT: lateral pterygoid muscle

5. Reconstruction of skull base with endonasal technique

In the past, craniotomy for CSF leakage and reconstruction of skull base defect commonly utilized vascularized pericranial or fascial flap harvested from skull. In this new era of

endoscopy, with external scar and need for some brain retraction, craniotomy for CSF leak repair has been preserved for those who failed endonasal endoscopic surgery. Upon access from skull base, similar to approaches with violation of dura and arachnoid membranes, CSF leak is one of the most common complications reported by many endoscopic series. However, few studies found that the incidence of CSF leakage from conventional surgery was not less frequent than endoscopic method. Among endoscopic procedures, the probability for CSF leakage is usually higher for the extrasellar lesions than limited pituitary-sellar surgery. The postresection communication between intracranial and nasal cavity must be thoroughly repaired to prevent any possibility of intracranial infection. For small defects, repair is accomplished independently of techniques for reconstruction.[15, 16] Conversely, larger defects, particularly for the high flow CSF leak, need a vascularized mucosal flap reconstruction in addition to a multilayer closure (Figure 28). It has been proven to yield better outcome with the incidence of CSF leakage < 5%.[17, 21] The advent of new technique for the intranasally harvested vascularized mucosal flap has been popularized. It has become well-known as the Hadad-Bassagasteguy flap (HBF).[22] The flap was developed from the mucoperiosteum and mucoperichondrium of the nasal septum that is supplied by the nasoseptal artery (Figures 29, 30, 31, 32, 33, 34). This reconstruction technique has improved the outcome of endonasal endoscopy for the skull base. Although the endoscopic skull base surgery via the endonasal corridor has the potential contamination from the sinonasal tract, the incidence of intracranial infections is still relatively low. The common intracranial infections are meningitis and intracranial abscess that have been reported in various incidences among the endoscopic series from less than 1% up to 10%,[23, 27] while the traditional approaches had the higher incidences from 15–30%.[28, 29] The intracranial infections were associated with the intradural resection, and some studies stated that they were related to the refractory postoperative CSF leak. Perioperative antibiotic prophylaxis is recommended to prevent the intracranial infections.

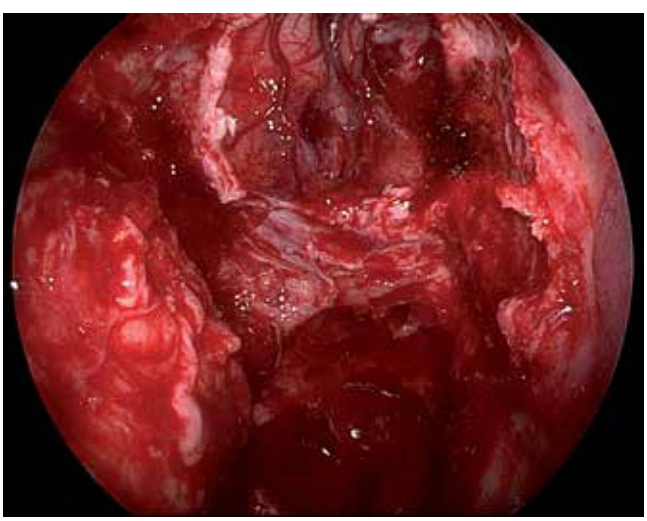

Figure 28. Endoscopic view of cribiform defect in pediatric patient after resection of fibro-osseous lesion.

http://dx.doi.org/10.5772/60556

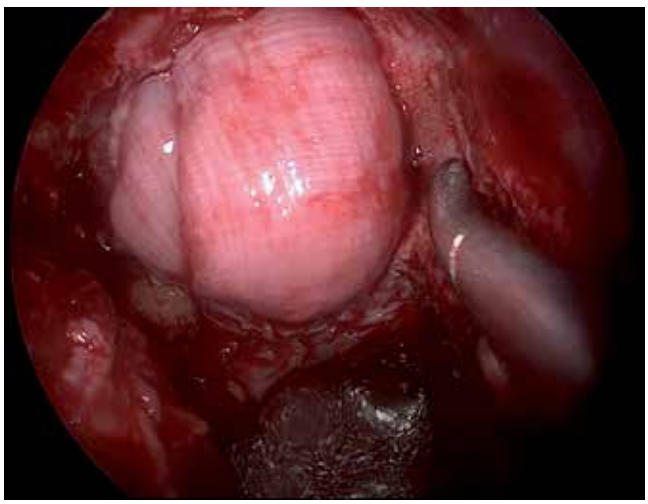

Figure 29. Endoscopic view of the same patient in Figure 28. The defect was reconstructed with multiple layers (fat graft and two layers of fascia lata).

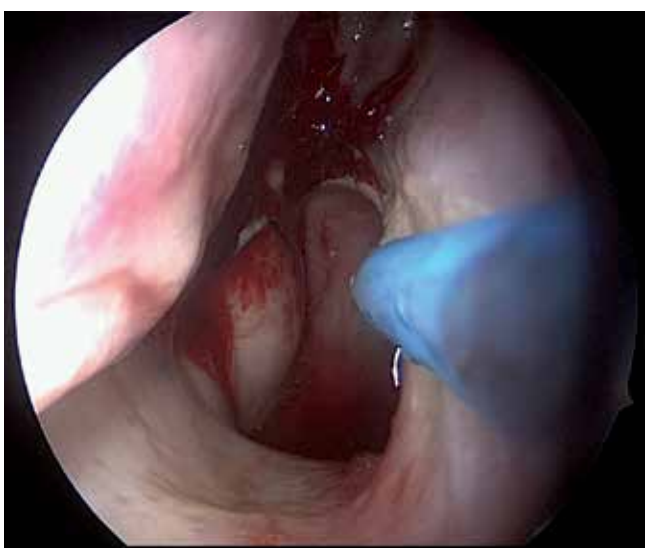

Figure 30. Endoscopic view, inferior incision for creation of nasoseptal flap is illustrated. This inferior incision typically starts at the roof of nasopharynx then advances anteriorly to mucocutaneous junction of nasal septum. Superior incision (not pictured) ideally starts at inferior level of sphenoid natural ostium and moves anteriorly to mucocutaneous junction of nasal septum.

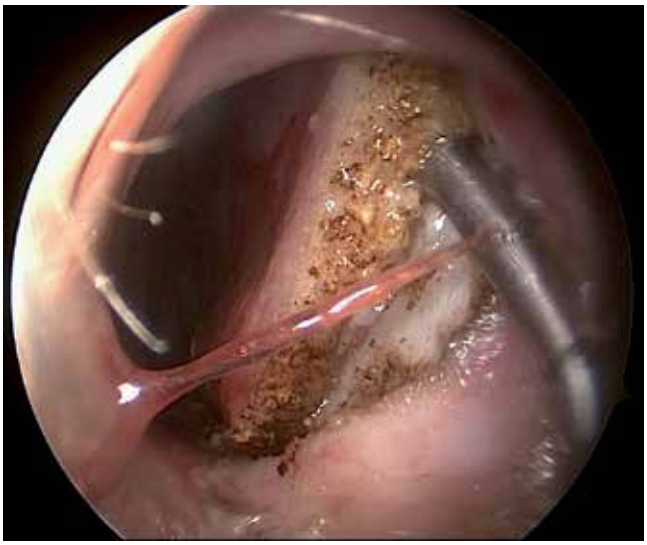

Figure 31. Endoscopic view of same patient in Figure 30. The superior and inferior incision will be connected by a vertical incision at mucocutaneous junction. Submucoperichondrium dissection should proceed from anterior to posterior toward its pedicle at the nasopharynx.

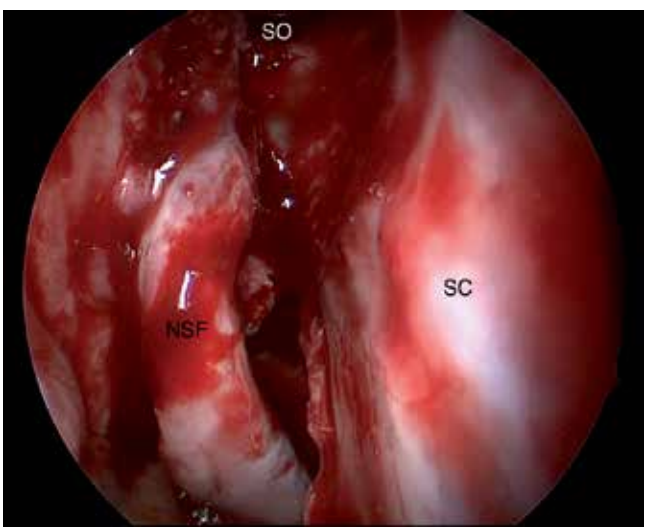

Figure 32. Endoscopic view of same patient in Figure 30. After elevation of nasoseptal flap, the pedicle is protected at posterior to preserve arterial supply by septal branch of sphenopalatine artery. NSF: nasoseptal flap SC: septal cartilage SO: sphenoid ostium

http://dx.doi.org/10.5772/60556

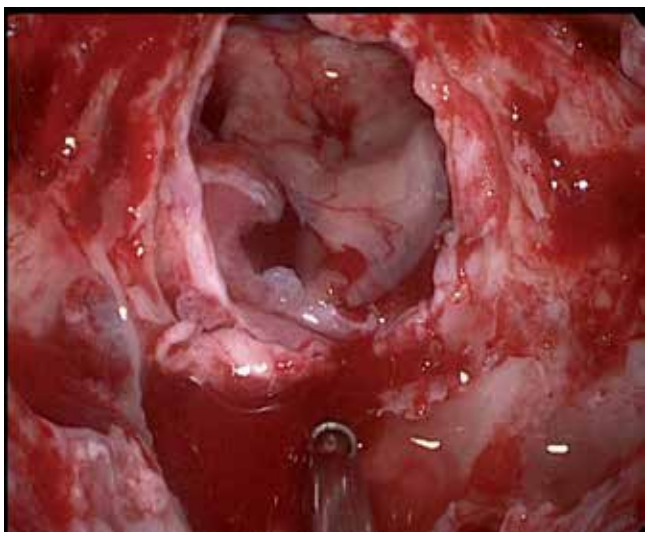

Figure 33. Endoscopic view of same patient in Figure 30 demonstrates the large skull base defect at sellar and planum after craniopharyngioma removal.

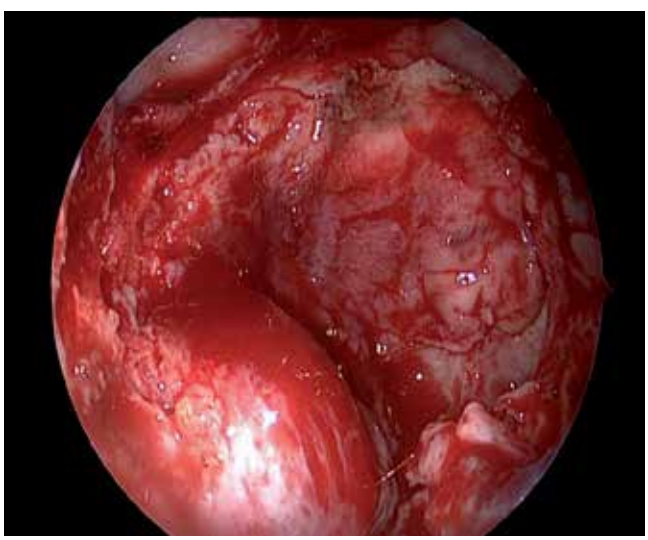

Figure 34. Endoscopic view of same patient in Figure 30. The nasoseptal flap was placed over the defect area after inlay placement of fat.

6. Surgical complications and morbidities

As mentioned earlier, although endoscopic skull base surgery creates direct communication between intracranial and nasal compartment, the incidence of intracranial infections is relatively low. Reports of the postoperative incidence of intracranial infection varied from less than 1% up to 10%.[23, 27]

Vascular injury during endoscopic procedures can be catastrophic, in particular when it involves the ICA. The ventral perspective of ICA that is perceived via endoscopic view is less familiar to surgeons than transcranial procedures. Higher rate of the ICA injury was more commonly associated with paramedian coronal plane dissection. Complete understanding of the ICA pathway and its surgical landmarks together with advanced intraoperative image-guided technology can minimize this feared intraoperative vascular complication. Fortunately, major ICA injury is uncommon with overall incidence of 0.9%. Experienced surgeons with multidisciplinary team approach as well as efficient instruments must be prepared to promptly deal with this critical event.[27] Though the ideal concept for management of an injured artery is to maintain lumen patency of the vessel, it is, unfortunately, extremely difficult to achieve in real situation. Direct repair with suture is close to impossible given the narrow corridor in light of profuse hemorrhage. Although several hemostatic agents or patches have varying success in damage control, at least temporarily, from our experience, crushed muscle has been the best. When all attempts fail, nasal packing is performed. Subsequently, angiographic study of the ICA is necessary. In some, balloon occlusion test is advocated in the preoperative plan in selected patients who carry high risk of vascular complications. Previous surgery or irradiation as well as tumor encasing ICA have been found to be factors predicting arterial injury.

Intraoperative neural injury from endoscopic series has been reported, with lower incidence than the traditional techniques. In addition, its majority was transient. The most commonly injured nerve was the CN VI. This could be related to its poor tolerance for manipulation.[27] Electromyographic cranial nerve monitoring during the surgery can signal surgeons of proximity to cranial nerves while dissecting a lesion. Dissection beyond the lateral limit of given cranial nerves is principally contraindicated for the endoscopic approach. Therefore, combined approaches from traditional craniotomy may occasionally be required for an extensive pathology.

The lower rate of overall complications from endonasal endoscopic approach seems more encouraging than the traditional techniques. Nevertheless, specialized training to gain experiences in this complex anatomical area along with advanced technological equipment is essential to surgeons to overcome obstacles in the course of his/her learning curve. With increased experience after several cases, the incidences of complication should typically approach acceptable reported incidence.

Over the past few decades, many authors have reported the feasibility and safety in the clinical uses of pure endoscopy in treatment of skull base pathologies. Understandably, with shorter follow-up time, endoscopic endonasal surgery cannot perfectly prove its efficacy, namely the long-term oncological control and functional outcome that has been its common target for criticism.

The general principle to achieve the oncological control is the complete resection of the tumor. The malignant pathologies, the surgical margins need to be extended. Via endoscopic approach, the en bloc tumor removal at the invasion site has been considered more fundamental than the en bloc resection of the entire tumor. The intraoperative frozen section is a tool to confirm the surgical margin after the en bloc resection at the tumor invasion site. The tumors arising in the sinonasal cavities usually have some parts situated in the air-filled space. The floating tumors in the cavities can be debulked in order to allow the surgeons comfortably insert the surgical instruments through the limited space and gain access to manage the tumors. At present, there is limited data to evaluate the oncological recurrence and disease-free survival rate. Many authors reported a small number of patients in the series of endonasal endoscopic surgery for skull base lesions for whom the oncological outcomes were favorable and comparable to the open techniques with lesser morbidities.[30, 33]

Although most of the surgeons have been experienced with the excellent functional outcomes and quality of life of the patients who underwent the endonasal endoscopic surgery, the published data has been limited. The obviously favorable outcomes include faster recovery without external scar and that the patients can regain normal or near-normal functions. The endonasal endoscopic skull base surgery has many steps of operation that can affect the patient's life in different ways. The further subanalysis of quality of life in each aspect of the procedure can lead to development of the completed data in the endoscopic surgical field.

7. Conclusion

Endoscopic endonasal surgery is challenging and dynamic. Coupling between the adjustments of the endoscopic lens position to acquire optimal view and the movement of instruments to provide the surgical freedom in the limited space requires tremendous experience and teamwork. It delivers enormous advantages for the various skull base pathologies which surgical corridor provides the most direct access to the ventral cranial base area. Proper selection of patients for endoscopic approach is crucial to achieve good outcome while avoiding untoward events. Comprehensive knowledge in complex skull base anatomy, training in advanced and high-volume institutes, advanced surgical technologies and strong teamwork are the keystones to gain the most benefit from this surgical method.

Author details

Boonsam Roongpuvapaht[1*], Kangsadarn Tanjararak[1] and Ake Hansasuta[2]

*Address all correspondence to: boonsamr@yahoo.com

1 Department of Otolaryngology Head and Neck Surgery, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Thailand

2 Division of Neurosurgery, Department of Surgery, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Thailand

References

[1] Messerklinger W: Diagnosis and endoscopic surgery of the nose and its adjoining structures. Acta Otorhinolaryngol Belg 1980;34:170–176.

[2] Wigand ME: Transnasal ethmoidectomy under endoscopical control. Rhinology 1981;19:7–15.

[3] Kennedy DW: Functional endoscopic sinus surgery: technique. Arch Otolaryngol 1985;111:643–649.

[4] Stammberger H: Endoscopic endonasal surgery – concepts in treatment of recurring rhinosinusitis. I. Anatomic and pathophysiologic considerations. Otolaryngol Head Neck Surg 1986;94:143–147.

[5] Stammberger H: Endoscopic endonasal surgery – concepts in treatment of recurring rhinosinusitis. II. Surgical technique. Otolaryngol Head Neck Surg 1986;94:147– 156.

[6] Stammberger H, Posawetz W: Functional endo- scopic sinus surgery: concept, indications and results of the Messerklinger technique. Eur Arch Otorhinolaryngol 1990;247:63–76.

[7] Duffner F, Freudenstein D, Wacker A, Straub Duffner S, Grote EH: 75 years after Dandy, Fay and Mixter – looking back on the history of neuroendoscopy. Zentralbl Neurochir 1998;59:121–128.

[8] Harris LW: Endoscopic techniques in neurosurgery. Microsurgery 1994;15:541–546.

[9] Carrau RL, Jho HD, Ko Y: Transnasal-transsphenoidal endoscopic surgery of the pituitary gland. Laryngoscope 1996;106:914–918.

[10] Jho HD, Carrau RL: Endoscopy assisted transsphenoidal surgery for pituitary adenoma: technical note. Acta Neurochir (Wien) 1996;138:1416–1425.

[11] Jho HD, Carrau RL, Ko Y, Daly MA: Endoscopic pituitary surgery: an early experience. Surg Neurol 1997;47:213–222; discussion 222–223.

[12] Kassam AB, Snyderman CH, Mintz A, Gardner P, Carrau RL: Expanded endonasal approach: the rostrocaudal axis. Part I. Crista galli to the sella turcica. Neurosurg Focus 2005;19:E3.

[13] Kassam AB, Snyderman CH, Mintz A, Gardner P, Carrau RL: Expanded endonasal approach: the rostrocaudal axis. Part II. Posterior clinoids to the foramen magnum. Neurosurg Focus 2005;19(1):E4.

[14] Kassam AB, Gardner P, Snyderman CH, Mintz A, Carrau RL: Expanded endonasal

[15] approach: fully endoscopic, completely transnasal approach to the middle third of

[16] the clivus, petrous bone, middle cranial fossa, and infratenporal fossa. Neurosurg Focus 2005;19(1):E6.

[17] Hegazy HM, Carrau RL, Snyderman CH, Kassam AB, Zweig J: Transnasal endoscopic repair of

[18] cerebrospinal fluid rhinorrhea: a meta-analysis. Laryngoscope 2000;110(7): 1166–1172.

[19] Senior BA, Jafri K, Benninger M: Safety and efficacy of endoscopic repair of CSF leaks and encephaloceles: a survey of the members of the American Rhinologic Society. Am J Rhinol 2001;15(1):21–25.

[20] Kassam AB, Thomas A, Carrau RL, Snyderman CH, Vescan A, Prevedello D, et al.: Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. Neurosurgery 2008; 63(1 suppl 1):ONS44–ONS53.

[21] Zanation AM, Carrau RL, Snyderman CH, Germanwala AV, Gardner PA, Prevedello DM, et al.: Nasoseptal flap reconstruction of high flow intraoperative cerebral spinal fluid leaks during endoscopic skull base surgery. American Journal of Rhinology & Allergy 2009;23(5):518–521.

[22] Shah RN, Surowitz JB, Patel MR, Huang BY, Snyderman CH, Carrau RL, et al.: Endoscopic pedicled nasoseptal flap reconstruction for paediatric skull base defects. Laryngoscope 2009;119(6):1067–1075.

[23] El Sayed IH, Roediger FC, Goldberg AN, Parsa AT, McDermott MW: Endoscopic reconstruction of skull base defects with the nasal septal flap. Skull Base: An Interdisciplinary Approach 2008;18(6):385–394.

[24] Harvey RJ, Nogueira JF, Schlosser RJ, Patel SJ, Vellutini E, Stamm AC: Closure of large skull base defects after endoscopic transnasal craniotomy. Clinical article. Journal of Neurosurgery 2009;111(2):371–379.

[25] Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al.: A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. Laryngoscope 2006;116:1882–1886.

[26] Cappabianca P, Cavallo LM, Colao A, De Divitiis E: Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. J Neuro- surg 2002; 97:293–298.

[27] Dehdashti AR, Ganna A, Karabatsou K, Gentili F: Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 2008; 62:1006–1017.

[28] Frank G, Pasquini E, Doglietto F, Mazzatenta D, Sciarretta V, Farneti G, et al.: The endoscopic extended transsphenoidal approach for craniopharyngiomas. Neurosurgery 2006; 59 (1 Suppl 1):ONS75–ONS83.

[29] Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E: The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. Neurosurgery 2006; 59 (1 Suppl 1): ONS50–ONS57.

[30] Kassam AB, Preveldello DM, Carrau RL, et al.: Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients. J Neurosurg

[31] 2011;114:1544–1568.

[32] Sen C, Triana A: Cranial chordomas: results of radical excision. Neurosurg Focus 2001;10(3):E3.

[33] Feiz-ErfanI, Han PP, Spetzler RF, Horn EM, Klopfenstein JD, Porter RW, et al.: The radical transbasal approach for resection of anterior and midline skull base lesions. J Neurosurg 2005;103:485–490.

[34] Stammberger H, Anderhuber W, Walch C, et al.: Possibilities and limitations of endoscopic management of nasal and paranasal sinus malignancies. Acta Otorhinolaryngol Belg 1999;53:199– 205.

[35] Casiano RR, Numa WA, Falquez AM: Endoscopic resection of esthesioneuroblastoma. Am J Rhinol 2001;15:271.

[36] Castelnuovo PG, Delu G, Sberze F, et al.: Esthesioneuroblastoma: Endonasal endoscopic treatment. Skull Base 2006;16:25–230.

[37] Snyderman CH, Carrau RL, Kassam AB, et al.: Endoscopic skull base surgery: principles of endonasal oncological surgery. Journal of Surgical Oncology 2008;97:658–664.

Chapter 13

Endoscopic Skull Base Surgery in the Pediatric Patient

Patrick C. Walz, Charles A. Elmaraghy and
Kris R. Jatana

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60555

Abstract

Pathology along the anterior and posterior skull base has long posed challenges to surgeons due to the difficulty accessing these locations and complexity of the surrounding neurovascular anatomy. Initial surgical management of these disorders included open craniofacial approaches and/or craniotomy and these approaches are still utilized today for selected cases. However, advances in the later half of the 20th century in optics, endoscope design, and high definition digital images allowed the development of microscopic and, more recently, endoscopic approaches to the skull base. This technology was initially developed and used in adults, but has been adapted over time for use in the pediatric patient. In this chapter, the salient points regarding pediatric endoscopic skull base surgery will be reviewed to provide the reader a framework for understanding the indications, pertinent anatomy, preoperative evaluation, and intraoperative management of skull base pathology, highlighting challenges and circumstances unique to the pediatric population.

Keywords: skull base, pediatric surgery

1. Introduction

Pathology along the anterior and posterior skull base has long posed challenges to surgeons due to the difficulty of accessing these locations and the complexity of the surrounding neurovascular anatomy. Initial surgical management of these disorders included open craniofacial approaches and/or craniotomy, and these approaches are still utilized today for

select cases. However, advances in the later half of the 20th century in optics, endoscope design, and high-definition digital images allowed the development of microscopic and, more recently, endoscopic approaches to the skull base. This technology was initially developed and used in adults, but has been adapted over time for use in the pediatric patient. In this chapter, the salient points regarding pediatric endoscopic skull base surgery will be reviewed to provide the reader a framework for understanding the indications, pertinent anatomy, preoperative evaluation, and intraoperative management of skull base pathology, highlighting the challenges and circumstances unique to the pediatric population.

2. History of endoscopic skull base surgery

Transnasal access to the skull base was introduced over a century ago by Schloffer, and Hirsch and Cushing respectively popularized the sublabial and transnasal approaches [1–3]. After Cushing's initial experience with transsphenoidal pituitary surgery, he turned to the subfrontal intracranial approaches [2]. The intracranial approaches remained popular until the introduction of the operating microscope in the 1960s allowed for the refinement of the transseptal transsphenoidal approach [4]. While modest efforts were made in addressing the anterior skull base and clival pathology endonasally with the microscope, it was not until the advent of the endoscope that the field expanded its scope to address pathology outside the sella, extending from the crista galli to the foramen magnum [4, 5]. In the 1990s endoscopic endonasal approaches to address pituitary lesions and cerebrospinal fluid leaks were proposed, which led to the gradual expansion of the field [6–11]. In 2005, the Center for Cranial Base Surgery at the University of Pittsburgh published several landmark papers highlighting the expanded endonasal endoscopic approaches to the skull base [4, 5, 12] and the use of these techniques has expanded steadily since the early 2000s. One key point emphasized by the Pittsburgh collaborative was the idea of "team surgery" in which the neurosurgeon and otolaryngologist—head and neck surgeon work simultaneously throughout all phases of the procedure [4]. With this binostril, four-handed approach, the surgeons can both visualize and manipulate the full extent of the midline skull base. In the last decade, the extent of the expanded endonasal approaches have continued to grow, pushing the limits of endonasal access anteriorly, laterally, superiorly, and posteriorly.

3. Applications to pediatric patients

The use of expanded endonasal endoscopic approaches in pediatric populations also developed as the field expanded. The application of open skull base approaches in the pediatric patient was described following its use in adults [13, 14]. The earliest case reports focusing on the use of endoscopic skull base surgery in children were published in the late 1990s [10, 11, 15] and steadily increased in the following decades. Though the techniques of endoscopic skull base surgery were carried on to the pediatric population, there has been limited publication on the topic compared to adult literature. There are several case reports outlining the use of

http://dx.doi.org/10.5772/60555

endoscopic techniques in the management of congenital meningoencephaloceles [16-19], benign tumors [20, 21], and bony lesions [22]. As juvenile nasopharyngeal angiofibroma (JNA) is exclusive to the adolescent age group, endoscopic management of this lesion is more widely described [15, 23-28]. There have also been several case series highlighting the application of endoscopic skull base surgery in the pediatric patient [29-31]. In Kassam et al.'s 2007 review, access to the entire skull base via a fully endoscopic approach demonstrated multiple advantages of over the previously utilized open approaches for these lesions. Key advantages discussed included minimal disruption of growth centers, lack of brain retraction with associated morbidity, and improved pituitary stalk visualization and potential preservation of the pituitary function [30].

4. Key differences between pediatric and adult skull base surgery

Though the general principles of endoscopic skull base surgery remain the same for both adults and pediatric patients, some critically important differences must be carefully considered in the pediatric patient preoperatively. These differences center around the development and aeration of the paranasal sinuses, size constraints encountered in the pediatric nose, and concern regarding skull base growth centers. A more complete review of developmental anatomy as it relates to endoscopic skull base surgery is described later in this chapter. Regarding size constraints, it is generally accepted that the nasal aperture is of sufficient size at the age of 6–7 years to accommodate a binostril endoscopic skull base approach [32]. Prior to this age, the interpyriform distance can preclude the introduction of endoscopes and instruments together and must be addressed on a case-by-case basis. Even with adequate nasal access, the intercavernous carotid distance may preclude adequate access in pediatric patients [32, 33] and must be evaluated preoperatively, especially if sellar or suprasellar access is the goal of the procedure. Lastly, the pediatric skull base is a dynamic structure and continues to expand and remodel until it reaches adult configuration following puberty. Careful attention must be paid to minimize disruptions to skull base growth centers in the prepubertal patient to abate growth disruptions [33, 34].

5. Developmental anatomy review

5.1. Sinonasal

First noted in the fourth week of development, the nasal capsule's lateral walls enlarge and fold by the ninth week, forming six ethmoturbinals, all derived from ectoderm from the frontonasal process. The first ethmoturbinal becomes the uncinate process while the second develops into the ethmoid bulla. The developmental end point of the third ethmoturbinal is the ground lamella of the middle turbinate and the fourth ethmoturbinal becomes the superior turbinate. The fifth and sixth ethmoturbinals may regress or fuse to become a supreme turbinate.

The four paired paranasal sinuses each have a distinct developmental trajectory. The maxillary sinuses project from the ethmoid infundibulum between the first and second ethmoturbinals and are first noted at week 9 of development. Present at birth, the maxillary sinus expands most significantly between ages 0–3 and 6–12, reaching adult size at approximately age 18. The ethmoid sinuses are also present at birth and continue to mature in an anterior to posterior fashion in the first 12 years of life. The frontal sinus is last to begin development in the fourth month of gestation as a superior evagination of the frontal recess. However, the frontal sinus is not distinguishable radiographically until approximately the third year of life and does not reach the frontal bone until age 5. The frontal sinus reaches adult size toward the end of puberty and can continue to aerate the frontal bone throughout adult life [35–37]. The sphenoid sinus is of primary importance in the endoscopic skull base surgery. It is first noted in the fourth week of gestation as an evagination from the sphenoethmoid recess and slowly aerates over the first 10–15 years of life. Aeration begins in the inferior and anterior aspect of the sinus and extends posteriorly and superiorly such that the dorsum sellae is last to aerate. At age 6–7, the sphenoid face is typically fully pneumatized and the planum is aerated in the majority of the patients. By age 10, the clival recess is typically pneumatized but dorsum sellae is infrequently pneumatized, 16% of the time [32, 33].

5.2. Sella and Skull Base

The sella itself divides the anterior and posterior skull base. The skull base develops primarily from cartilaginous precursors, which ossify over the first two decades of life. The anterior skull base derives from a neural crest cell origin while the clivus and other posterior skull base structures have paraxial mesodermal origins [32, 35]. The remaining details of skull base development and ossification are beyond the scope of this chapter and are described elsewhere [35].

6. Surgical indications

The indications for surgical intervention at the skull base are fairly limited in terms of broad categories and include cerebrospinal fluid (CSF) leak, neoplasms, and congenital abnormalities. While the surgical goal with CSF leak is clear, when addressing neoplasms, the role of surgery can range from biopsy for diagnosis to surgical debulking to complete resection (clear margins) and is largely dependent upon the pathology being addressed and the location. In the setting of malignancies such as rhabdomyosarcoma or other sarcomas, the role of surgery may vary, and it becomes important to pre-operatively define the goals of the surgical treatment in these cases.

6.1. Cerebrospinal fluid leak

Whether spontaneous, posttraumatic, or iatrogenic, the presumptive diagnosis of CSF leak is made when persistent clear rhinorrhea is identified (Figure 1). The confirmation of CSF is made with a laboratory analysis for β-2 transferrin. Imaging with CT can identify areas of bony

http://dx.doi.org/10.5772/60555

discontinuity. In cases where the location is difficult to assess, MR or CT myelography can be performed to help localize the area of CSF egress. The initial approach to CSF leaks often entails conservative management with lumbar drain placement and medical management to decrease intracranial pressures with surgery reserved for refractory leaks or high-flow CSF leaks not likely to resolve with conservative management alone.

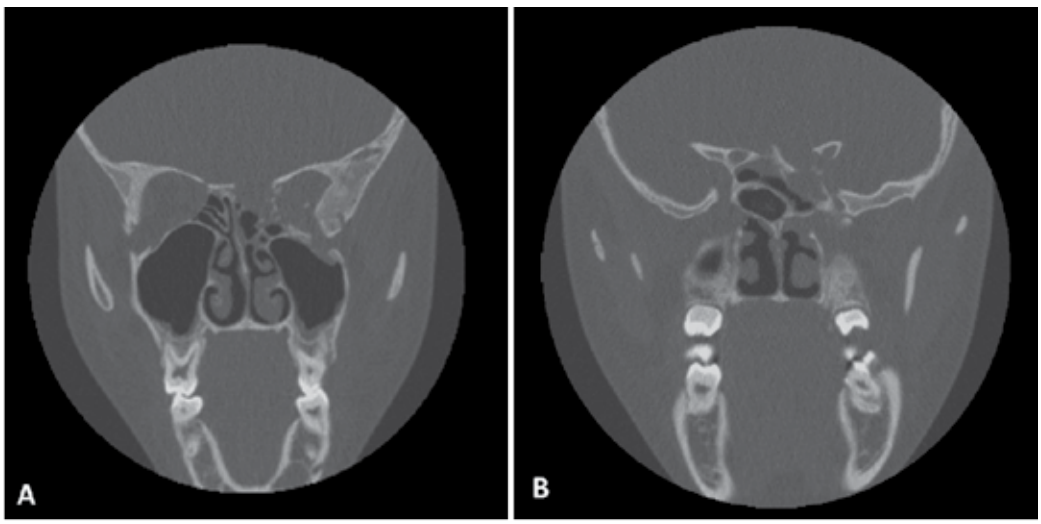

Figure 1. CSF leak from multiple skull base fracture: (A) cribriform plate and (B) left sphenoid. This was successfully repaired using transnasal endoscopic techniques.

6.2. Neoplasms

Neoplasms can vary in both pathology and presentation. A thorough discussion of each tumor is beyond the scope of this chapter, and tumors have been widely described in the literature. A brief overview of the various pathologies and their most common locations are shown in Table 1. Figure 2 demonstrates a rhabdomyosarcoma.

Lesion	Category	Location
Fibrous dysplasia	Benign neoplasm	Anterior skull base, perisellar, clivus
Fibro-osseous tumors	Benign neoplasm	Anterior skull base
Pituitary adenoma	Benign neoplasm	Sella
Craniopharyngioma	Benign neoplasm	Sella
Chordoma	Benign neoplasm	Clivus
Schwannoma	Benign neoplasm	Clivus, infratemporal fossa

Lesion	Category	Location
Juvenile nasopharyngeal angiofibroma (JNA)	Benign neoplasm	Pterygopalatine fossa, infratemporal fossa
Glomus jugulare	Benign neoplasm	Clivus
Chondrosarcoma	Malignant neoplasm	Clivus
Esthesioneuroblastoma	Malignant neoplasm	Anterior skull base
Meningoencephalocele	Congenital abnormality	Anterior skull base, perisellar, clivus
Glioma	Congenital abnormality	Anterior skull base, perisellar, clivus
Nasal dermoid	Congenital abnormality	Anterior skull base
Cerebrospinal fluid leak	Iatrogenic, traumatic, idiopathic	Anterior skull base, perisellar, clivus

Table 1. Differential Diagnosis of Pediatric Skull Base Abnormalities

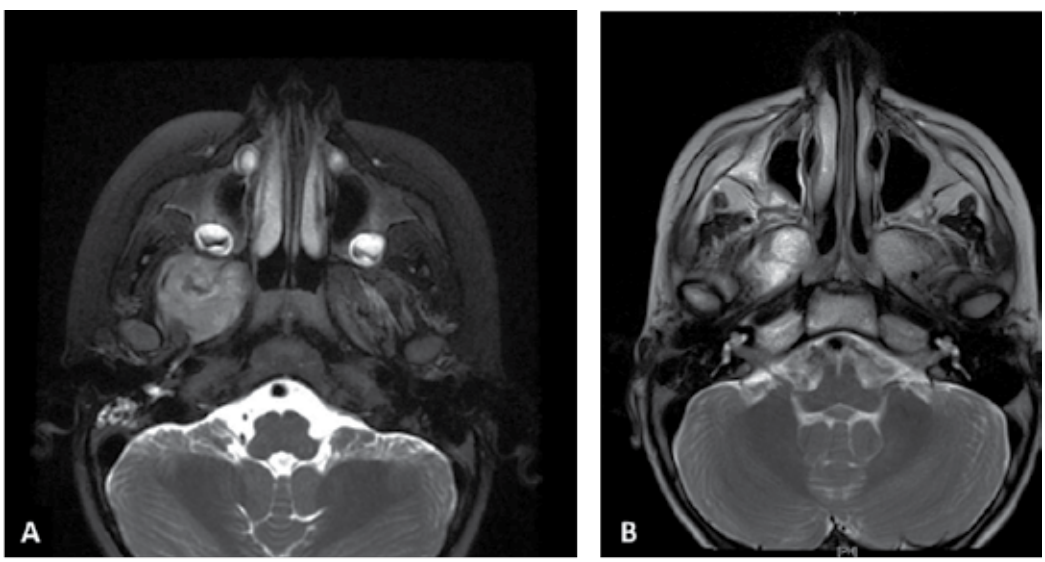

Figure 2. A 3-year-old male with right pterygopalatine fossa rhabdomyosarcoma. (A) Pretreatment and (B)Post-chemoradiation therapy. Given some residual enhancing tissue, multiple endoscopic biopsies were performed after treatment to ensure no residual disease and were consistent with radiation changes.

7. Developmental abnormalities

Disruptions in the normal development of skull base structures may result in meningoencephaloceles (Figure 3), gliomas, and nasal dermoids. These lesions can be characterized by their location of origin and contents [18, 38–40], but all share a common origin in aberrant ectodermal differentiation and/or closure of the neural folds [18].

http://dx.doi.org/10.5772/60555

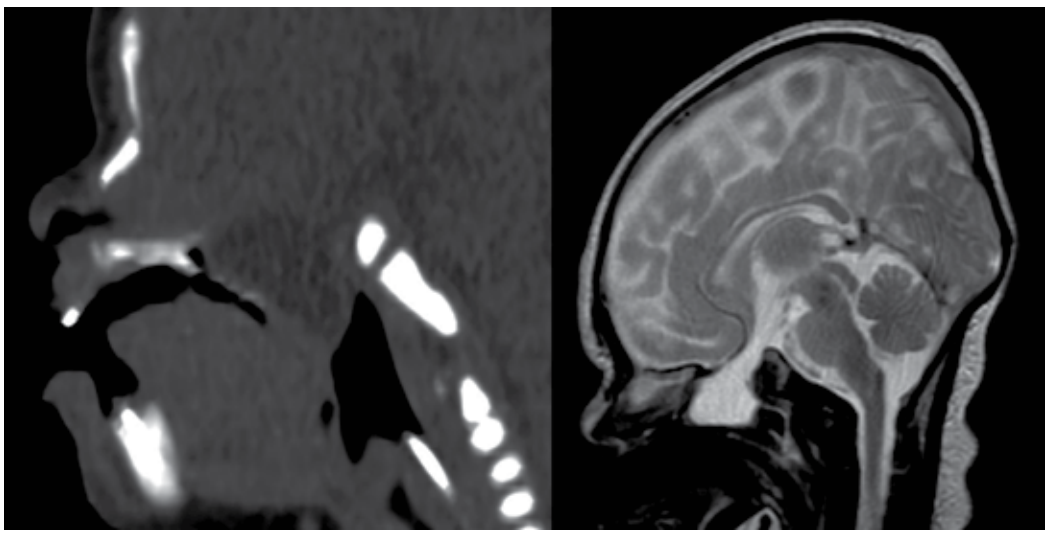

Figure 3. Newborn child with a large sphenoethmoidal meningoencephalocele. With a skull base defect this large in a newborn, open repair is the only option. The left image is a sagittal noncontrasted CT scan performed for initial diagnosis. On the right is a T2-weighted sagittal MRI to further characterize this lesion, identifying no neural components within the sac.

8. Clinical presentation

Clinical presentation varies for each lesion and is dependent upon the lesion's origin and compression of the surrounding structures. Pituitary lesions that are hormonally active may also present with endocrine disturbances [30]. Compression of the optic nerve or tracts may present with unilateral or bilateral ocular symptoms depending upon the location of the compression [30]. Sellar lesions extending into the cavernous sinus may compress cranial nerves 3 or 4 and the ophthalmic branch of 5 or 6. The sixth nerve is the most sensitive to compression and lateral rectus palsy is often the first presenting symptom of cavernous sinus involvement. Clival lesions may also compress cranial nerves 9, 10, 11, and rarely 12. Meningoceles and meningoencephaloceles may present with a nasal obstruction, which can become more significant with agitation due to increased intracranial pressure expanding the extracranial portion of the sac [18]. Osseous lesions such as fibrous dysplasia may present with narrowing of neural foramina or with externally visible skeletal deformities depending upon the bone(s) involved [30]. Vascular lesions, such as juvenile nasopharyngeal angiofibroma, present with unilateral nasal obstruction and epistaxis, a diagnosis exclusive to adolescent males. Other presenting symptoms may include headache, proptosis, nausea, hydrocephalus, or nondescript symptoms such as drooling or torticollis [29, 30].

9. Preoperative assessment

9.1. History and physical examination

A thorough history and physical examination is essential for any patient. Careful attention to progression and timing of symptoms in the history and to the cranial nerve examination on physical examination can help to direct the differential diagnosis. Nasal endoscopy can be helpful in the presence of nasal obstructive symptoms or olfactory disturbances to assess intranasal involvement and characterize the extent and potential origin of any lesion in question. A biopsy of any pediatric nasal mass should *not* be performed prior to imaging, and if tissue diagnosis is needed, the procedure should be done in the operating room. Figures 4 and 5 demonstrate examination findings as to why imaging is necessary prior to interventions. In the setting of CSF leak, a thorough history of any traumatic injuries or previous sinonasal or intracranial procedures is valuable in helping to identify the etiology and potential location of the CSF leak.

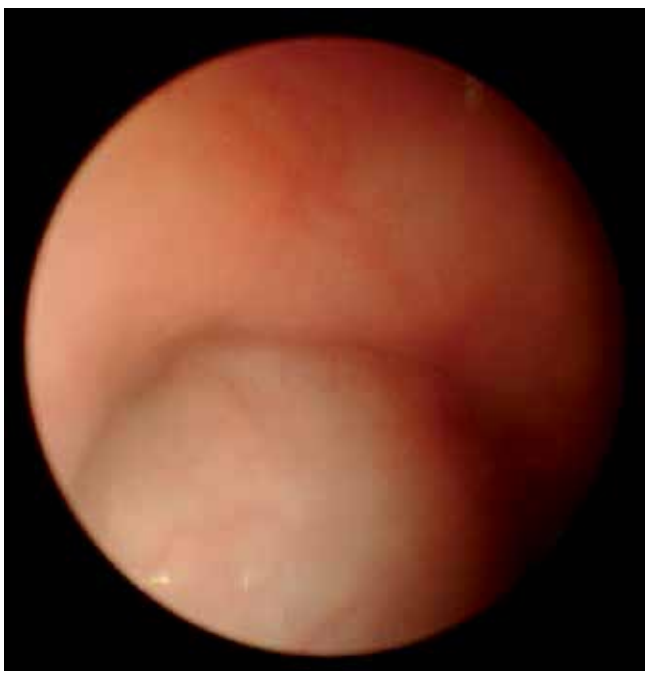

Figure 4. Right nasal endoscopy in an infant with nasal obstruction symptoms, which was found to have a nasopharyngeal/skull base mass, consistent with a meningocele on MRI imaging.

9.2. Labs

Laboratory assessment is pathology-driven. In the presence of a suspected hormonally active pituitary lesion, a "pituitary panel" may be ordered to assess cortisol response, TSH, prolactin,

http://dx.doi.org/10.5772/60555

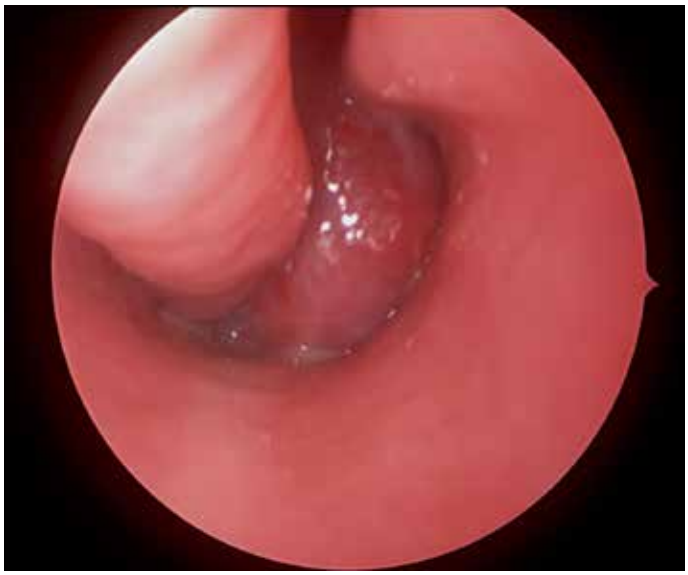

Figure 5. Right nasal endoscopy demonstrating a sinonasal mass in a 15-year-old male, consistent with JNA.

FSH, and LH levels. In the presence of a vascular tumor, preoperative hematologic labs including blood typing and cross-matching are indicated, as surgical resection can entail significant blood loss requiring transfusion.

9.3. Imaging

Preoperative imaging is integral to surgical planning in any endoscopic skull base procedure. Imaging allows the characterization of the extent of the lesion and enables identification of carotid artery involvement or encasement, intracranial extension, orbital invasion, and infratemporal fossa extension.

9.3.1. Computed Tomography (CT)

CT provides excellent bony detail and can help to identify stable surgical landmarks for intraoperative use. While soft tissue resolution is not as clear as with magnetic resonance imaging (MRI), the overall extent of the lesion can be characterized. While a non-contrast CT scan is often the first performed test with which a skull base lesion is diagnosed, a scan for intraoperative surgical navigation use should be a fine-cut, axially oriented contrast-enhanced scan that includes the maxillary alveolus, nasal tip, and extends superiorly far enough to capture the optic tracts or cranial aspect of the lesion in question, whichever is more cranial. With these images, coronal and sagittal reconstructions can be created and the images can be loaded onto a surgical navigation system for intraoperative use. The use of contrast clearly outlines the carotid arteries in their tortuous course through the clivus and cavernous sinus.

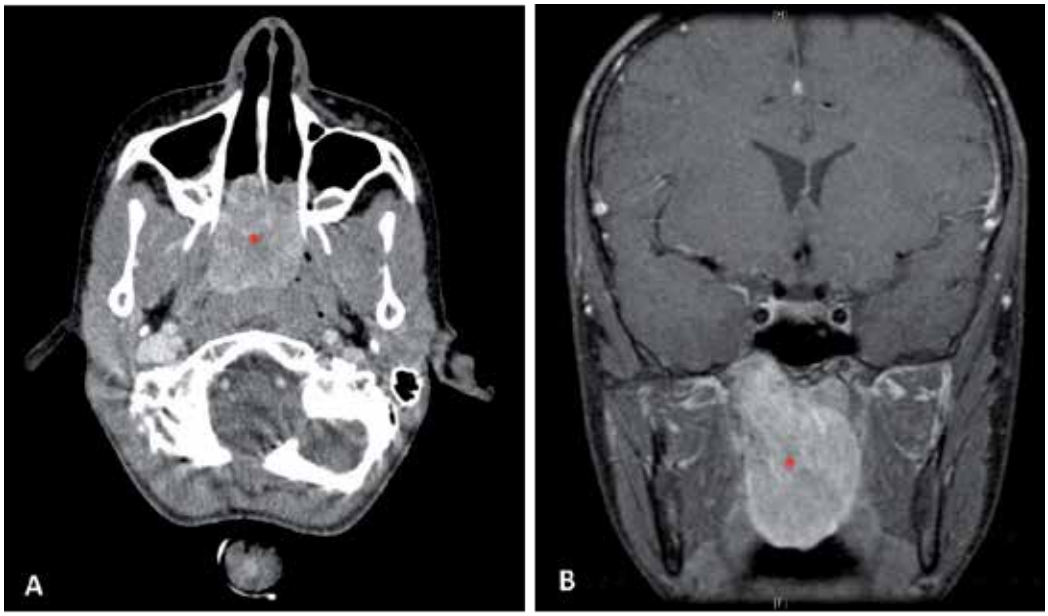

Figure 6. (A) Axial CT scan showing JNA, arising from right sphenopalatine foramen. (B) Coronal MRI showing proximity to sphenoid sinus and extension into nasopharynx and oropharynx.

9.3.2. Magnetic Resonance Imaging (MRI)

MRI utilizes the differential response of hydrogen atoms to magnetic fields to generate images with higher resolution of the soft tissue characteristics than can be obtained with CT. Whereas inspissated secretions within a sinus would be indistinguishable from the tumor invasion of that sinus on a CT scan, these two scenarios are clearly differentiated with a MRI scan. With the use of multiple image sequences including T1-weighted, T2-weighted, and contrast enhancement, soft tissue interfaces can be delineated and signal characteristics can narrow the differential diagnosis of the lesion. MRI images can also be utilized for intraoperative surgical navigation and should be formatted in a similar fashion to that described for CT. Of note, MRI requires the patient to remain still for up to 2 hours to obtain multiple sequences without image distortion from movement. For this reason, pediatric patients often require sedation or general anesthesia to obtain adequate images. Figure 6 shows a JNA and Figure 7 a meningocele on MRI.

9.3.3. Angiography and possible embolization

Several circumstances benefit from preoperative angiography and possible endovascular embolization (Figure 8). First, in the case of juvenile nasopharyngeal angiofibroma, preoperative embolization 24–48 hours prior to the planned resection enables significant devascularization of the contribution of the external carotid artery to the lesion, which leads to a decreased intraoperative blood loss [41, 42], though this finding is seen primarily when the

http://dx.doi.org/10.5772/60555

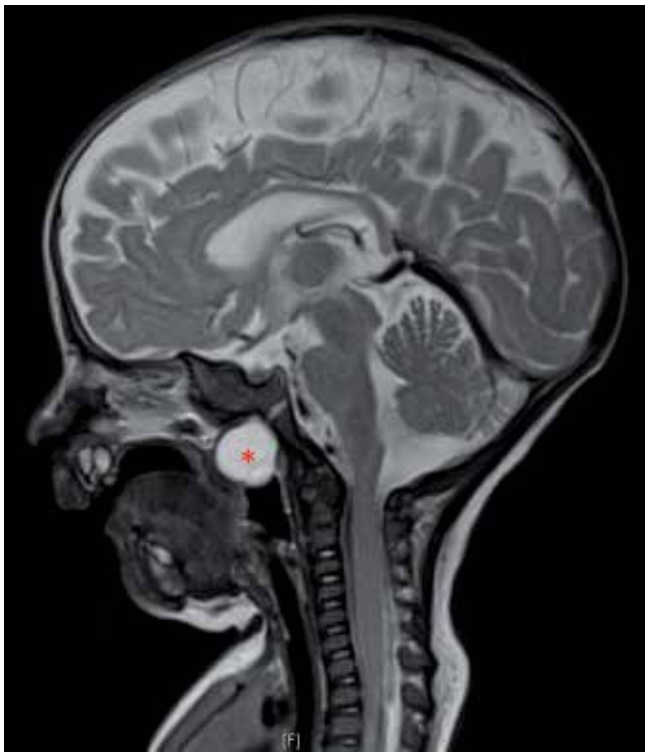

Figure 7. A nasopharyngeal/skull base mass, consistent with a meningocele in an infant who presented with nasal obstruction and feeding difficulties as seen with T2-weighted sagittal MRI scan.

JNA is supplied exclusively by the external carotid system. Nevertheless, preoperative angiography identifying the location of internal carotid feeding vessels can guide dissection for vascular control [24].

The second situation in which preoperative angiography and possible embolization are beneficial is in the case of suspected carotid artery encasement. In this situation or similar situations in which the integrity of the carotid wall is in question, angiography allows for preoperative characterization of the intracranial blood flow and affords the opportunity to perform balloon occlusion testing to determine the impact of unilateral carotid sacrifice [43]. As this intervention still carries a 6% risk of cerebrovascular accident [44, 45], the decision for preoperative occlusion is reserved for situations in which intraoperative carotid injury is highly likely.

10. Surgical planning

Pediatric skull base surgery is a rapidly developing field involving multiple specialties. The collaboration between otolaryngology, neurosurgery, neuroradiology (including interven-

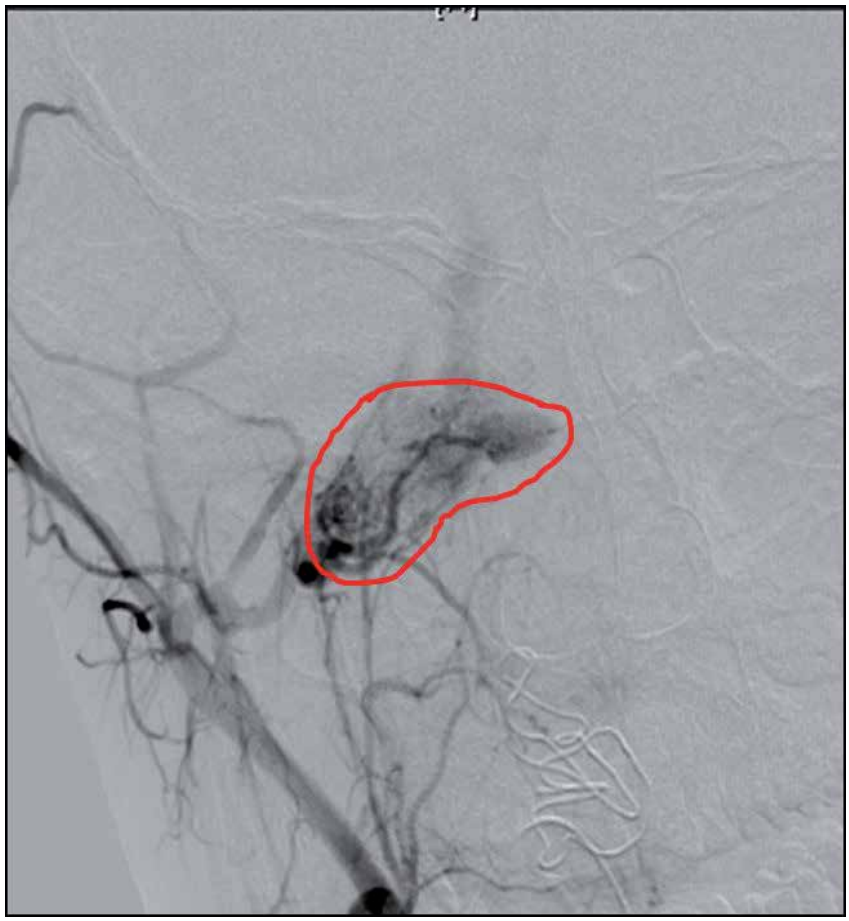

Figure 8. Angiography of external carotid artery, showing tumor blush. Blood supply from sphenopalatine artery, a branch of the internal maxillary artery. This vessel was embolized preoperatively by the interventional radiology team. Sometimes there can be feeding vessels off branches of the ipsilateral internal carotid artery or contralateral carotid system so complete assessment is necessary.

tional radiology), critical care, pediatrics, nursing, and surgical staff has evolved to allow for the optimal management of pediatric patients. Technology has driven the advancement of the management of neoplasms of the nasal cavity and skull base. Endoscopy has become critical in surgical approaches and its applications to neoplasms of the nasal cavity have been a major advance in otolaryngology and neurosurgery. Endoscopic approaches are the standard of care for most sinonasal problems and the instrumentation has been well developed.

10.1. Endoscopes and camera

Currently, rigid endoscopes are the standard for use during a surgical intervention. Although flexible scopes are used and available, they are typically used for diagnostic purposes. Rigid endoscopes allow visualization with a wide field of view, as opposed to a microscope. The

http://dx.doi.org/10.5772/60555

rod-lens rigid scopes are the most commonly used as they provide a high-quality image. They consist of three parts: shaft, glass fiber bundle, and optics. The endoscopes are available in various diameters but the goal is to use the largest diameter that can be accommodated. The most common rigid scopes are 2.7 and 4 mm in diameter. Endoscopes larger than 4 mm become difficult to use transnasally with other instruments. Although the use of a smaller diameter endoscope allows for greater degrees of freedom, the amount of light transmitted is decreased, which can make surgery at the skull base difficult. Several different angles are available with rigid endoscopes. Standard endoscopes part of a surgical set should include 0°, 30°, 45°, and 70°. The more angled the scope, the more disorienting the image may be. The standard approach is with the 0° to maintain the image projected as anatomic and changing to angled endoscopes as necessary. The endoscopes are attached to a light source that should be xenon. The cable is made of glass fibers, which poorly transmit heat, preventing the endoscope from causing thermal damage. The endoscopes are also attached to a HD camera that transmits the images to be projected onto monitors strategically placed in the operating room. The advancement in image technology has allowed for high resolution necessary to operate around neurovascular structures.

10.2. Surgical instrumentation

Instruments designed for endoscopic sinus surgery are standard for use in skull base procedures. The design of the instruments allows for intranasal use with a concurrent endoscope. The instruments are inserted transnasally and the nostril is used as a fulcrum about which the endoscope is pivoted. Angled instruments are part of a standard set for anterior skull base and frontal sinus and are used often with the angled endoscopes. Straight instruments are designed to be low profile and allow for easy visualization of the tip of the instrument and the endonasal structures. Instruments including curettes, elevators, scissors, forceps with and without cutting capability, and drills are each designed specifically for working intranasally. Powered drills and microdebriders are used often to remove tissue for access and for the resection of certain lesions. Bipolar forceps are designed with appropriate size and length to work intranasally in order to achieve hemostasis. Monopolar cautery is to be avoided close to neurovascular structures but is integral to harvesting of pedicled vascular flaps.

10.3. Use of surgical navigation systems

The use of intraoperative surgical navigation systems has become commonplace in the field of endoscopic skull base surgery. Often neoplasms obscure normal landmarks, and navigation systems allow for greater spatial awareness during these dissections. Image-guidance systems use both optical and magnetic field technology and both have advantages and disadvantages. Image guidance for skull base is typically based on preoperative high-resolution CT scans but can be fused with MRI images as well. The information provided by this technology has been referred to as "image guidance," but this is a misnomer when utilized appropriately. The use of surgical tools connected to the navigation system allows additional confirmation of visually identified landmarks and assists in determining the extent of resection in complex skull base lesions or anatomy in a field distorted by the disease process or previous surgery [46]. In the

management of CSF leaks, intraoperative surgical navigation can confirm visually suspected areas of bony dehiscence. While not a sine qua non in endoscopic skull base surgery, intraoperative surgical navigation is a valuable tool that should be utilized when available. Of utmost importance in the use of these systems is ensuring accurate registration of the patient and to periodically confirm accuracy with navigation to known landmarks [46, 47].

11. Operating suite

Endoscopic skull base surgery is often a two-surgeon procedure and the setup of the operating room must accommodate this arrangement. With two surgeons on either side of the patient with a surgical technician, a nurse, or an assistant, it is necessary to have the patient in the 180° position from anesthesia. Communication with the anesthetist for the control of the airway is necessary as these procedures can take several hours. Establishing and securing the airway, intravenous vascular access, arterial lines, and monitors are necessary to prevent adjustments or interruptions of the procedure. The head of the patient can be elevated slightly as well to facilitate venous drainage. The HD monitors and image guidance system can be integrated in the operating room and each surgeon and assistant must have a monitor in a direct line of site. This necessitates a suite designed with multiple monitors linked to a central control center. The instrument table and assistant should be positioned equidistant from the two surgeons without physical obstruction to passing of instruments.

12. Surgical approaches

Total endoscopic approach is appropriate for many sinonasal tumors. The neoplasms can be removed through one or both nostrils depending on the extent. The use of both nostrils requires a trans-septal approach either by creating a perforation or by resection of the posterior septum. The choice is dependent on the location of the tumor. The uninostril (through one nostril) procedure is less destructive to normal structures but can limit the degrees of freedom and the number of instruments placed in the nose. Binostril approach allows for one surgeon to work bimanually and another surgeon to control the suction and the endoscope. For extensive lesions, this is the preferred technique.

The approaches have variations in the trajectory to the skull base and four different endonasal approaches have been described: transnasal, transethmoid, transsphenoidal, and transpterygoidal.

The transnasal approach does not traverse the sinuses but essentially keeps the septum and the middle turbinate as the boundaries. Lesions of the cribiform plate such as encephaloceles can be managed in this manner. In addition, clival and odontoid pathology can be addressed through the choana.

http://dx.doi.org/10.5772/60555

The transethmoid approach requires a total ethmoidectomy and can expose the skull base from the frontal to sphenoid sinus. The lamina papyracea is exposed as well. This approach is useful for encephaloceles or orbital apex lesions.

The transsphenoidal approach requires removal of the anterior face of the sphenoid and often the sphenoid rostrum and posterior septum. Removal of the middle turbinate can increase the degrees of freedom and optimize visualization. The transsphenoid approach is used for sellar, pituitary, upper clival, and cavernous sinus lesions. Figure 9 shows a craniopharyngioma which was managed in this manner.

The transpterygoidal approach requires a corridor through the maxillary sinus and the removal of the posterior wall of the sinus. A medial maxillectomy and ligation of the sphenopalatine artery are necessary which is often done with JNA resection (Figure 10). This approach is useful for the infratemporal fossa. Figure 11 required the pterygoid bone to be removed for access to a rhabdomyosarcoma.

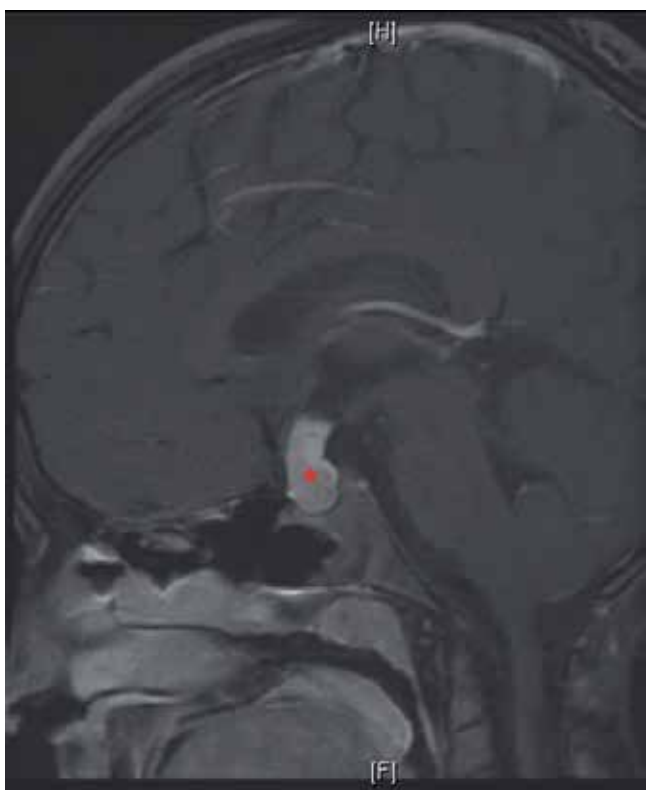

Figure 9. A 13-year-old male who presented with new onset vision loss was found to have a craniopharyngioma on this sagittal T1-weighted MRI with contrast. An endoscopic, transsphenoid approach was performed for removal.

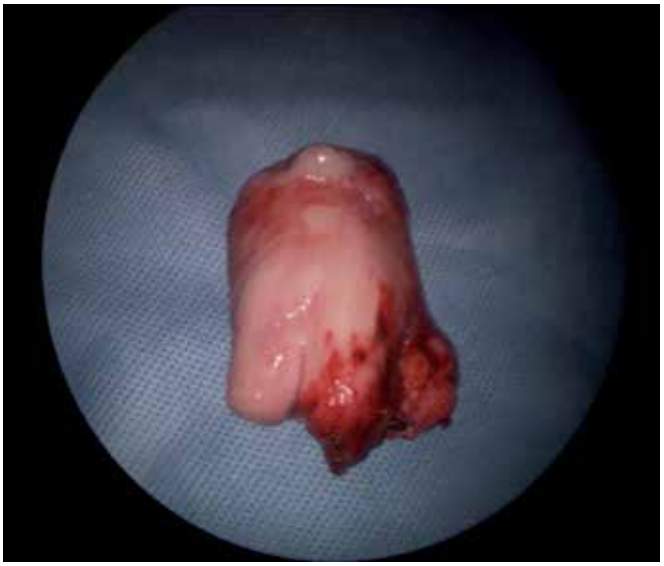

Figure 10. A JNA s/p endoscopic resection from pterygopalatine fossa, nasal cavity, sphenoid sinus, and nasopharynx.

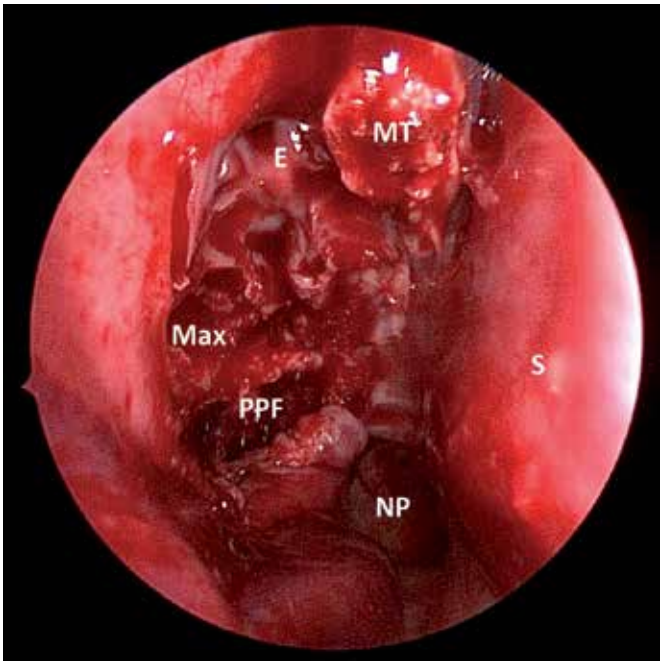

Figure 11. Right endoscopic view for approach and biopsy of pterygopalatine fossa mass that was a rhabdomyosarcoma. The pterygoid bone had to be drilled down medially in order to get access. S=septum, NP=nasopharynx, MT=middle turbinate, E=ethmoid, Max=maxillary sinus, PPF=pterygopalatine fossa.

http://dx.doi.org/10.5772/60555

13. Hybrid approaches

Although many lesions can be approached by endoscopic-only approach, certain lesions necessitate a hybrid approach with the use of open techniques. Lateral lesions of the infratemporal fossa may require a Caldwell-Luc combined with transpterygoid. Lesions that are far anterior, such as neoplasms at the anterior pyriform aperture or of the frontal sinus, often require a hybrid approach. Other open approaches such as bicoronal, lateral rhinotomy, or palatal split (Figure 12) can be used depending on the extent of surgery, and endoscopy can be a useful adjunct to ensure complete resection. Transcervical endoscopic-assisted surgery of the skull base can be a useful adjunct to access difficult-to-reach areas as shown in Figure 13.

Endoscopic-assisted trephination of the frontal sinus with a repair of an isolated posterior table fracture with CSF leak has been described in a pediatric patient. This avoided the need for bicoronal flap and craniotomy for open repair [48].

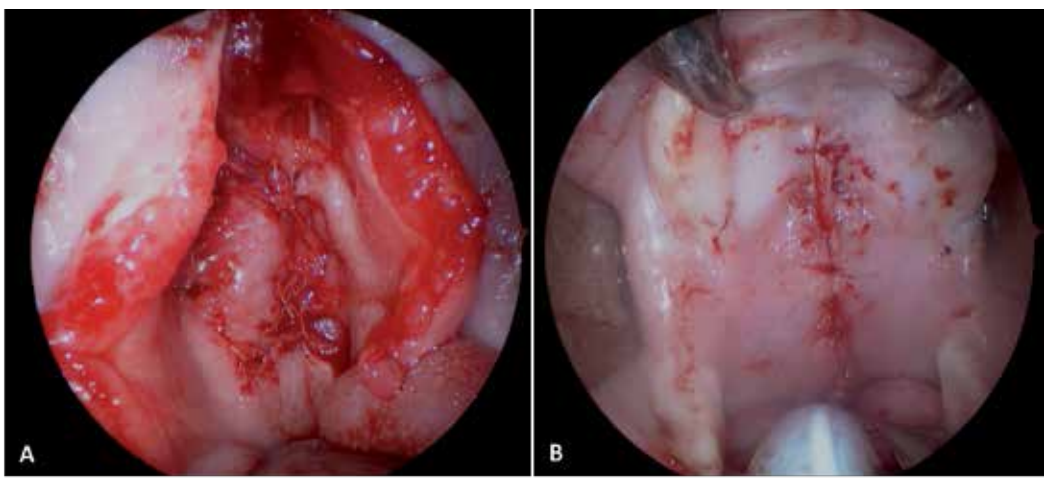

Figure 12. (A) Endoscopic-assisted, transpalatal/palatal split approach to skull base in nasopharynx for excision of meningocele in an infant. The palatal flaps are retracted and a vascularized pharyngeal flap was placed over a cartilage graft on right side of superior nasopharynx to repair the bony defect in skull base. (B) Multilayer repair of the palate.

14. Staging surgery

The goal of any approach to a neoplasm is ideally total removal of the tumor with minimal damage to normal structures. The strategy for sinonasal tumors must be defined and the pathology often dictates the approach. Some tumors such as juvenile nasopharyngeal angiofibroma can be diagnosed by imaging. Other lesions need initial biopsy. Biopsy of the sinonasal tumors requires adequate imaging to ensure safety of any disruption of the tumor as intracranial extent or prominent vascularity can make limited biopsies potentially dangerous. Consultation with the radiologist can be helpful for planning.

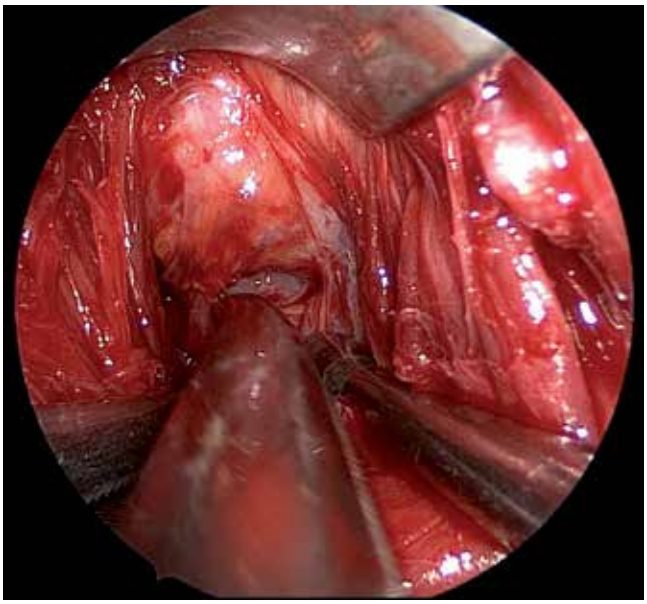

Figure 13. Endoscopic-assisted, transcervical approach to the left parapharyngeal space and skull base for excision of recurrent pleomorphic adenoma after initial excision at age 15. The mass was dissected from the skull base with endoscopic visualization and avoidance of mandibulotomy and plating for surgical access.

Due to the proximity of neurovascular structures such as the optic nerve and carotid artery, incomplete resection may be necessary to preserve function or prevent injury. Certain benign pathologies such as fibrous dysplasia can make this a feasible strategy. In addition, lymphomas and certain subtypes of rhabomyosarcoma are chemotherapy- and radiation-sensitive, and the morbidity of complete resection makes this approach prohibitive.

15. Reconstructive options

The endoscopic approach to resection of sinonasal tumors is only feasible because reconstructive techniques exist to maintain the separation between the nonsterile nasal cavity and the sterile intracranial contents. As the extent of tumors and surgical approach varies, so do the reconstructive techniques. The goal is to create a water- and air-tight closure to prevent CSF leak and meningitis. Preoperative planning includes reconstruction for the anticipated defect. Reconstruction may span from no reconstruction with healing by secondary intention to the use of vascularized grafts. Ideally, the reconstruction should match the tissue resected. If a large bony defect is encountered, rigid support may be necessary to prevent herniation of intracranial contents. Bone, cartilage, fascia, mucosa, and fat can be used as autologous free grafts.

Free tissue grafts can be harvested intranasally. If middle turbinate is resected, the bone and mucosa can be used for small defects of the skull base. The middle turbinate free graft can be

http://dx.doi.org/10.5772/60555

filleted open and used as an onlay graft. If a more rigid tissue is necessary, cartilage can be harvested from the nasal septum and used as an inlay graft to repair skull base defects. Multilayered grafts that combine various types of tissues are often used. Once the grafts are placed, fibrin-sealing agents can be placed over the surface of the reconstruction to provide a watertight closure.

One of the recent advances in skull base reconstruction is the use of the pedicled nasal septal flap, which is based on the posterior septal artery [49]. This flap is useful for defects with a concomitant CSF leak. Planning of this flap is important specifically with transsphenoidal approaches in order not to damage the blood supply to this flap. Other intranasal flaps include the inferior turbinate flap or middle turbinate flap, both based on branches of sphenopalatine artery. Scalp flaps include the pericranial flap (supraorbital and supratrochlear arteries), temporoparietal fascia flap (superficial temporal artery), or temporalis muscle flap (deep temporal arteries).

All of the skull base reconstructions require some packing to keep contact and ensure adequate healing. A combination of absorbable and non-absorbable packing can be used. Typically, gel foam is placed over the reconstruction, and non-absorbable splint or packing is used for additional reinforcement.

15.1. Use of lumbar drain

In the past, lumbar drains were routinely used for decompression during an endoscopic repair of a CSF leak. With the advent of reliable vascularized flaps, the need for lumbar drainage has decreased. It is now thought that low-flow CSF leaks can generally be managed surgically without the use of the lumbar drain, while in some high-flow leaks it should be considered [50].

16. Postoperative management

After surgical intervention, close monitoring in the hospital setting is recommended for pediatric patients. Depending on the extent of surgery and need for hemodynamic monitoring, and frequent neurologic checks, the patient may go to the pediatric ICU setting as opposed to a traditional floor. When there is any violation of the dura or CSF leak repair is preformed intraoperatively, there should be close observation for any CSF rhinorrhea. Activity levels should be determined based on the extent of surgery. Stool softeners can help reduce straining, as constipation may increase intracranial pressure and a risk of CSF leak. Antibiotic prophylaxis postoperatively is considered in a setting of CSF leak repair [51] or when absorbable packing is used to reduce the risk of infection.

17. Surgical complications

There are several potential complications from endoscopic skull base surgery. Given the high vascularity of these operative sites, and even despite “near complete” embolization of a JNA,

there can be significant blood loss intraoperatively, which requires blood transfusion. In a pediatric patient, the decision to stage resection is sometimes made to avoid blood transfusion. A major vascular injury to the cavernous sinus, carotid artery at skull base, or intracranial hemorrhage can occur. Cerebral vascular accident or strokes can also occur. When the muscles of mastication are within the surgical field, trismus postoperatively can occur and patients should begin jaw-stretching exercises at the earliest stages. CSF leak can occur when the dura is violated, but the key is recognizing it and performing an endoscopic repair. The risk of meningitis is significantly reduced with prompt and proper repair of a CSF leak. Infections including sinusitis and meningitis are possible. Endocrinopathy can occur when the pituitary gland is involved. Altered olfaction can result from either a change in nasal airflow dynamics or injury to the olfactory bulb or other special sensory fibers within the nasal cavity. Other cranial nerve injuries, including vision loss or blindness, diplopia, dry eye symptoms, and facial numbness can also occur.

18. Conclusions

The use of pediatric endoscopic skull base surgery has continued to grow as techniques and technology pioneered in the adult population have been applied to children. The need for open surgical approaches has decreased with the advancement of endoscopic techniques that are now available to address pathologic conditions of the skull base in the pediatric population. Experienced surgical teams with multidisciplinary support at tertiary care pediatric facilities can best manage these young patients.

Author details

Patrick C. Walz, Charles A. Elmaraghy and Kris R. Jatana*

*Address all correspondence to: Kris.Jatana@nationwidechildrens.org

Department of Otolaryngology-Head and Neck Surgery, Nationwide Children's Hospital and Wexner Medical Center at Ohio State University, Columbus, Ohio, USA

References

[1] Cohen-Gadol AA, Liu JK, Laws ER, Jr. Cushing's first case of transsphenoidal surgery: the launch of the pituitary surgery era. Journal of Neurosurgery. 2005;103(3): 570–4. Epub 2005/10/21.

[2] Liu JK, Cohen-Gadol AA, Laws ER, Jr., Cole CD, Kan P, Couldwell WT. Harvey Cushing and Oskar Hirsch: early forefathers of modern transsphenoidal surgery. Journal of Neurosurgery. 2005;103(6):1096–104. Epub 2005/12/31.

[3] Hirsch O. Endonasal method of removal of hypophyseal tumors. With a report of two successful cases. JAMA 1910;55:772–774.

[4] Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part I. Crista galli to the sella turcica. Neurosurgical Focus. 2005;19(1):E3. Epub 2005/08/05.

[5] Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part II. Posterior clinoids to the foramen magnum. Neurosurg Focus 2005;19(1):E4. Epub 2005/08/05.

[6] Zeitouni AG, Frenkiel S, Mohr G. Endoscopic repair of anterior skull base cerebrospinal fluid fistulas: an emphasis on postoperative nasal function maximization. The Journal of Otolaryngology. 1994;23(3):225–7. Epub 1994/06/01.

[7] Dodson EE, Gross CW, Swerdloff JL, Gustafson LM. Transnasal endoscopic repair of cerebrospinal fluid rhinorrhea and skull base defects: a review of twenty-nine cases. Otolaryngology—Head and Neck Surgery : Official Journal of American Academy of Otolaryngology—Head and Neck Surgery. 1994;111(5):600–5. Epub 1994/11/01.

[8] Miyagi A, Maeda K, Sugawara T. [Usefulness of neuroendoscopy and a neuronavigator for removal of clival chordoma]. No shinkei geka Neurological Surgery. 1998;26(2):169–75. Epub 1998/03/26.

[9] Lanza DC, O'Brien DA, Kennedy DW. Endoscopic repair of cerebrospinal fluid fistulae and encephaloceles. The Laryngoscope. 1996;106(9 Pt 1):1119–25. Epub 1996/09/01.

[10] Weiss DD, Robson CD, Mulliken JB. Transnasal endoscopic excision of midline nasal dermoid from the anterior cranial base. Plastic and Reconstructive Surgery. 1998;102(6):2119–23. Epub 1998/11/12.

[11] Van Den Abbeele T, Elmaleh M, Herman P, Francois M, Narcy P. Transnasal endoscopic repair of congenital defects of the skull base in children. Archives of Otolaryngology—Head & Neck Surgery. 1999;125(5):580–4. Epub 1999/05/18.

[12] Kassam A, Snyderman CH, Carrau RL, Gardner P, Mintz A. Endoneurosurgical hemostasis techniques: lessons learned from 400 cases. Neurosurgical Focus. 2005;19(1):E7. Epub 2005/08/05.

[13] Teo C. Complete endoscopic removal of colloid cysts: issues of safety and efficacy. Neurosurgical Focus. 1999;6(4):e9. Epub 2006/05/10.

[14] Gil Z, Constantini S, Spektor S, Abergel A, Khafif A, Beni-Adani L, et al. Skull base approaches in the pediatric population. Head Neck. 2005;27(8):682-9. Epub 2005/06/16.

[15] Jorissen M, Eloy P, Rombaux P, Bachert C, Daele J. Endoscopic sinus surgery for juvenile nasopharyngeal angiofibroma. Acta Oto-Rhino-Laryngologica Belgica. 2000;54(2):201–19. Epub 2000/07/13.

[16] Gassab E, Krifa N, Kedous S, Zrig A, Hattab N, Harrathi K, et al. Endoscopic endonasal management of congenital intranasal meningocele in a 2-month-old infant. European Annals of Otorhinolaryngology, Head and Neck Diseases. 2013;130(6):345–7. Epub 2013/05/22.

[17] Kanowitz SJ, Bernstein JM. Pediatric meningoencephaloceles and nasal obstruction: a case for endoscopic repair. International Journal of Pediatric Otorhinolaryngology. 2006;70(12):2087–92. Epub 2006/10/31.

[18] Omar A. El-Banhawy ANH. Endoscopic endonasal excision of congenital midline meningoencephalocele in a 5-month infant. Int J Pediatr Otorhinolaryngol Extra. 2009;4:66–71. Epub September 20, 2008.

[19] Vidya Bhushan R, Balasubramany AM, Nandakumar R, Reynold, R. Endoscopic management of nasal encephalocele in a 4-month-old baby. Int J Pediatr Otorhinolaryngol Extra. 2014;9:67–9.

[20] Salmasi V, Reh DD, Blitz AM, Argani P, Ishii M, Gallia GL. Expanded endonasal endoscopic approach for resection of a skull base low-grade smooth muscle neoplasm. Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery. 2012;28(1):151–8. Epub 2011/11/02.

[21] Kanaan HA, Gardner PA, Yeaney G, Prevedello DM, Monaco EA, 3rd, Murdoch G, et al. Expanded endoscopic endonasal resection of an olfactory schwannoma. J Neurosurg Pediatr. 2008;2(4):261–5. Epub 2008/10/04.

[22] Salmasi V, Blitz AM, Ishii M, Gallia GL. Expanded endonasal endoscopic approach for resection of a large skull base aneurysmal bone cyst in a pediatric patient with extensive cranial fibrous dysplasia. Child's nervous system : ChNS: Official Journal of the International Society for Pediatric Neurosurgery. 2011;27(4):649–56. Epub 2010/12/07.

[23] Fyrmpas G, Konstantinidis I, Constantinidis J. Endoscopic treatment of juvenile nasopharyngeal angiofibromas: our experience and review of the literature. European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS). 2012;269(2):523–9. Epub 2011/07/27.

[24] Ballah D, Rabinowitz D, Vossough A, Rickert S, Dunham B, Kazahaya K, et al. Preoperative angiography and external carotid artery embolization of juvenile nasophar-

yngeal angiofibromas in a tertiary referral paediatric centre. Clinical radiology. 2013;68(11):1097–106. Epub 2013/08/06.

[25] Hackman T, Snyderman CH, Carrau R, Vescan A, Kassam A. Juvenile nasopharyngeal angiofibroma: the expanded endonasal approach. American Journal of Rhinology and Allergy. 2009;23(1):95–9. Epub 2009/04/22.

[26] Gallia GL, Ramanathan M, Jr., Blitz AM, Reh DD. Expanded endonasal endoscopic approach for resection of a juvenile nasopharyngeal angiofibroma with skull base involvement. Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia. 2010;17(11):1423–7. Epub 2010/08/17.

[27] Eloy P, Watelet JB, Hatert AS, de Wispelaere J, Bertrand B. Endonasal endoscopic resection of juvenile nasopharyngeal angiofibroma. Rhinology. 2007;45(1):24–30. Epub 2007/04/17.

[28] Douglas R, Wormald PJ. Endoscopic surgery for juvenile nasopharyngeal angiofibroma: where are the limits? Current Opinion in Otolaryngology & Head and Neck Surgery. 2006;14(1):1–5. Epub 2006/02/10.

[29] Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC, Gardner PA, Tyler-Kabara EC. Endoscopic endonasal skull base surgery in the pediatric population. Journal of Neurosurgery Pediatrics. 2013;11(3):227–41. Epub 2012/12/18.

[30] Kassam A, Thomas AJ, Snyderman C, Carrau R, Gardner P, Mintz A, et al. Fully endoscopic expanded endonasal approach treating skull base lesions in pediatric patients. Journal of Neurosurgery. 2007;106(2 Suppl):75–86. Epub 2007/03/03.

[31] Locatelli D, Rampa F, Acchiardi I, Bignami M, Pistochini A, Castelnuovo P. Endoscopic endonasal approaches to anterior skull base defects in pediatric patients. Child's nervous system: ChNS: Official Journal of the International Society for Pediatric Neurosurgery. 2006;22(11):1411–8. Epub 2006/06/30.

[32] Rastatter JC, Snyderman CH, Gardner PA, Alden TD, Tyler-Kabara E. Endoscopic Endonasal Surgery for Sinonasal and Skull Base Lesions in the Pediatric Population. Otolaryngologic Clinics of North America. 2015;48(1):79–99. Epub 2014/12/03.

[33] Tatreau JR, Patel MR, Shah RN, McKinney KA, Zanation AM. Anatomical limitations for endoscopic endonasal skull base surgery in pediatric patients. The Laryngoscope. 2010;120 Suppl 4:S229. Epub 2011/01/13.

[34] Lowlicht RA, Jassin B, Kim M, Sasaki CT. Long-term effects of Le Fort I osteotomy for resection of juvenile nasopharyngeal angiofibroma on maxillary growth and dental sensation. Archives of Otolaryngology—Head & Neck Surgery. 2002;128(8):923–7. Epub 2002/08/07.

[35] Gruber DP, Brockmeyer D. Pediatric skull base surgery. 1. Embryology and developmental anatomy. Pediatr Neurosurg. 2003;38(1):2–8. Epub 2002/12/12.

[36] Sadler T. Langman's medical embryology. Philadelphia: Lippincott Williams & Wilkins; 2009.

[37] Head and Neck Surgery—Otolaryngology. Bailey B, editor. Philadelphia: Lippincott Williams & Wilkins; 2001.

[38] Hoving EW. Nasal encephaloceles. Childs Nerv Syst. 2000;16(10-11):702–6. Epub 2001/01/11.

[39] Rahbar R, Resto VA, Robson CD, Perez-Atayde AR, Goumnerova LC, McGill TJ, et al. Nasal glioma and encephalocele: diagnosis and management. Laryngoscope. 2003;113(12):2069–77. Epub 2003/12/09.

[40] Campbell LR, Dayton DH, Sohal GS. Neural tube defects: a review of human and animal studies on the etiology of neural tube defects. Teratology. 1986;34(2):171–87. Epub 1986/10/01.

[41] Ungkanont K, Byers RM, Weber RS, Callender DL, Wolf PF, Goepfert H. Juvenile nasopharyngeal angiofibroma: an update of therapeutic management. Head & Neck. 1996;18(1):60–6. Epub 1996/01/01.

[42] Fagan JJ, Snyderman CH, Carrau RL, Janecka IP. Nasopharyngeal angiofibromas: selecting a surgical approach. Head Neck. 1997;19(5):391–9. Epub 1997/08/01.

[43] Risley J, Mann K, Jones NS. The role of embolisation in ENT: an update. The Journal of Laryngology and Otology. 2012;126(3):228–35. Epub 2011/12/17.

[44] Harada K, Morioka J, Higa T, Saito T, Fukuyama K. Significance of combining distal filter protection and a guiding catheter with temporary balloon occlusion for carotid artery stenting: clinical results and evaluation of debris capture. Annals of Vascular Surgery. 2012;26(7):929–36. Epub 2012/09/05.

[45] Linskey ME, Jungreis CA, Yonas H, Hirsch WL, Jr., Sekhar LN, Horton JA, et al. Stroke risk after abrupt internal carotid artery sacrifice: accuracy of preoperative assessment with balloon test occlusion and stable xenon-enhanced CT. AJNR: American Journal of Neuroradiology 1994;15(5):829–43. Epub 1994/05/01.

[46] Snyderman C, Zimmer LA, Kassam A. Sources of registration error with image guidance systems during endoscopic anterior cranial base surgery. Otolaryngology—Head and Neck Surgery : Official Journal of American Academy of Otolaryngology—Head and Neck Surgery. 2004;131(3):145–9. Epub 2004/09/15.

[47] Wiltfang J, Rupprecht S, Ganslandt O, Nimsky C, Kessler P, Schultze-Mosgau S, et al. Intraoperative image-guided surgery of the lateral and anterior skull base in patients with tumors or trauma. Skull Base: Official Journal of North American Skull Base Society. 2003;13(1):21–9. Epub 2005/05/25.

[48] Jatana KR, Ryoo C, Skomorowski M, Butler N, Kang DR. Minimally invasive repair of an isolated posterior table frontal sinus fracture in a pediatric patient. Otolaryngol-

ogy-Head and Neck Surgery : Official Journal of American Academy of Otolaryngology—Head and Neck Surgery. 2008;138(6):809–11. Epub 2008/05/28.

[49] Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. The Laryngoscope. 2006;116(10):1882–6. Epub 2006/09/28.

[50] Stokken J, Recinos PF, Woodard T, Sindwani R. The utility of lumbar drains in modern endoscopic skull base surgery. Current opinion in otolaryngology & head and neck surgery. 2015;23(1):78–82. Epub 2015/01/08.

[51] Prosser JD, Vender JR, Solares CA. Traumatic cerebrospinal fluid leaks. Otolaryngologic Clinics of North America. 2011;44(4):857–73, vii. Epub 2011/08/09.

Chapter 14

Skull Base Endoscopic-Assisted Surgery

Joachim M.K. Oertel and
Guilherme Ramina Montibeller

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60588

Abstract

Endoscopic-assisted surgery is becoming a more and more important tool in the neurosurgical armamentarium. This chapter provides a broad overview of the role of this technique in various skull base procedures. It starts with a historical perspective followed by a thorough exploration of the various principles and techniques for different indications. Additionally, the topics of "minimally invasive" techniques using "key hole" approaches are explained. At the end of this chapter, advantages and pitfalls with endoscopic assisted techniques are discussed.

Keywords: Endoscopic assisted skull base surgery, aneurysm clipping, vestibular schwannoma, key hole surgery

1. Introduction

The neuroendoscopic technique has its roots in the early 20th century, applied at the beginning to treat hydrocephalus with cauterization or removal of the choroid plexus [1, 2]. Pure endonasal endoscopic resection of pituitary tumors became more popular in the 1990s, and skull base endoscopy has made timid advances since then. Increased development in skull base endoscopy occurred just before 2005 [3]. The new generation of neuroendoscopes allowed neurosurgeons to use them in the subarachnoid space and to use their excellent light quality and optical resolution in the depth during microsurgical procedures [1, 4].

Nowadays the neuroendoscope is used in different intracranial procedures as the main visualization tool or as an additional device. In modern skull base surgery, it has a significant

supplementary value and has been used more and more frequently for different pathologies and in diverse occasions. Some advantages of the neuroendoscope for the skull base surgery are as follows:

a. Very good illumination

b. The possibility to demonstrate structures from a different angle ("look around the corner")

c. Less invasiveness by reduction of approach size and retraction of structures

Different from intraventricular endoscopy, there are no preformed cavities in skull base surgery, and the need of retraction of structures is not infrequent. Vestibular schwannomas, cerebellopontine angle meningiomas, trigeminal neuralgia, epidermoid tumors, hemifacial spasms, and aneurysms are some of the skull base pathologies in which the endoscope can be helpful giving additional information on the target. The possibility of introduction of the tip of the endoscope into deep areas and the use of different angle scopes widening the field of view permit the reduction of surgical trauma during the approach, by reduced retraction of structures.

The endoscopic-assisted technique is becoming a very powerful method to be added to the armamentarium of neurosurgical technologies in skull base surgeries. This chapter provides a broad overview of the role of this technique in a wide spectrum of skull base diseases, starting with a historical perspective of the evolution of the use of the endoscope in skull base surgery and followed by the exploration in depth of the principles and techniques of the different surgical methods. In addition, the topic of "minimally invasive" skull base surgery using "keyhole" approaches and finally the learning curve and complications associated with the application of these new techniques is discussed.

2. Evolution of neuroendoscopy

The name endoscope comes from two Greek words — endon that means within and skopein that means to view [5]. Along the years, this visualization instrument has been used to look inside every natural opening and cavity in the human body.

At the beginning, the direct visualization inside of the bladder, female genital organs, or the digestive tract using a speculum was restricted to a few centimeters. The view into deeper cavities was restricted by the difficulty of illumination and poor visual quality. The son of Italian immigrants and born in Mainz, Germany, in 1773, physician Philipp Bozzini constructed at the beginning of the 19th century what may be considered as a rudimental endoscope. This equipment consisted of a speculum with two chambers — one for the transmission of light and the other one for the visualization. Bozzini called this instrument "Lichtleiter" what in German means "light conductor" [2].

After several improvements and developments of this equipment in Germany and Austria, the serial production of cystoscopes began in the United States at the beginning of the 20th century. The initial use of this technique in neurosurgery has its roots in the early 20th century.

The urologist Victor Darwin L'Esspinasse and the neurosurgeon Allen Buckner Kanavel used for the first time an endoscope to perform the cauterization of the choroid plexus in two children with hydrocephalus in 1910 [1, 2].

Guiot et al. in Paris documented the first case of a pure transsphenoidal endoscopic resection of a pituitary tumor in 1962. This surgical technique became more popular, however, in the mid-1990s. After a short break, increased development of the endoscopy of the skull base could be observed again at the beginning of the 21st century. These advances were fruit of two important elements present at this time: technology and creativity [3]. Endoscopes with better light quality and capable of exceptional image reproduction allowed an excellent exposition of the deep surgical field in the skull base. New ideas and attempts to solve old problems as the restricted straight-line view of the microscope were responsible for additional discoveries in this field [1, 4].

Endoscopic skull base surgery techniques as the minimally invasive approaches, endoscopic-assisted surgery and full-endoscopic surgery are today in continuous development.

Advances of the neuroendoscopic equipment like the endoscope-integrated near-infrared indocyanine green video angiography for aneurysm surgery and the continuously variable-view rigid endoscope with possibility to alternate the view angle without the necessity of changing the scope just as well contribute to the rapid progress of skull base endoscopy [6-8]. In the same way, the combination with other known methods as robot-assisted neuroendoscopy and neuro-navigated endoscopy propel the progress of this technique.

3. Skull base surgery

Skull base surgery comprises the treatment of several pathologies that are located or have their source in the most inferior part of the cranial cavity. Because of the complex anatomy and important structures, approaches and operations in this region have always been challenging. Tumors, aneurysms, and neurovascular conflicts are the most frequent pathologies treated in this area. During the last decades, important developments in the skull base surgery were responsible for substantial reductions in the morbidity and mortality. Advancements of the intraoperative neuromonitoring, microsurgical techniques, and new imaging modalities were some of these developments [9]. The use of the endoscopic technique in this region began later on and is gradually increasing.

3.1. Goals of skull base surgery

Skull base pathologies may be very complex and the decision of the right treatment is not always so evident. In some cases, there is little or no doubt about what should be done. However, in many of these patients, different therapy options or no therapy at all ("wait and see") should be considered. So that the best advice may be given to a patient, the physician must have the knowledge concerning the natural history of the disease and also be up-to-date about the current and new treatment alternatives [10].

The goal of every medical treatment is of course the well-being of the patient. To achieve that, some objectives as tumor complete resection, partial resection, or simply biopsy for eventually further radio- or chemotherapy should be considered in different situations [11]. The skull base surgery aim should be very well analyzed in every case and the expectations of the patient need to be considered for the final decision of the therapy strategy.

The main objective during the surgery of tumors in this region is the complete removal with preservation of function provoking as little physical and mental pressure as possible to the person being treated. If total resection is not possible or represents a great risk of impairment of important functions as in some cases of sphenoid wing meningiomas, large vestibular schwannomas, or petroclival meningiomas, cytoreductive surgery as preparation for radiotherapy should be considered [12, 13]. In certain cases of elderly or, for example, patients with neurofibromatosis type 2, purely decompression may be the main goal of the operation [12, 14].

In most cases, however, the final goal is to achieve a complete tumor resection, aneurysm clipping, or neurovascular decompression with total neurovascular function preservation and minimal patient stress.

4. Clinical features

The clinical presentation of skull base pathologies is very variable, depending on the nature and location of the underlying cause. Cranial nerve dysfunction, cerebellar symptoms, hydrocephalus (e.g., in tumors of the posterior cranial fossa obstructing the 4th ventricle), and thunderclap headache (in patients with subarachnoid hemorrhage after aneurysm rupture) are some of the possible presentations. Furthermore, a considerable number of patients with a skull base disease are referred to a neurosurgical department with no complains and an incidental finding. The actual patient's complains and results expectations should be considered during decision and planning of the most appropriate treatment modality.

5. Diagnosis and neuroimaging

As said before, skull base pathologies are much diversified. The ideal image method should be elected depending on the current questions for each case.

Magnetic resonance imaging (MRI) is useful in almost every case due to its magnificent ability to demonstrate soft tissues. The routine T1-, T2-, and T1 with endovenous contrast injection-weighted images should be obtained in all three planes — axial, coronal, and sagittal — so that an accurate study of each case can be carried out. The fluid-attenuated inversion recovery (FLAIR) is a pulse sequence using an inversion recovery technique that nulls fluids. It is very sensitive to edema and some parenchymal abnormalities and can be used to indirectly demonstrate lesions that are not evident in other sequences. Diffusion weighted imaging (DWI) sequences are useful in differentiating epidermoid tumors, that are hyperintense due

its solid composition), from arachnoid cysts shown hypointense, demonstrating high diffusivity. Some authors still report about the importance of this sequence during the assessment of clival tumors, particularly in differentiating chordoma from chondrosarcoma [15]. The gradient echo sequence provides information about hemoglobin breakdown products and calcifications [16].

Computed tomography (CT) scan is the image of choice for demonstrating bony structures. Before surgeries involving the internal auditory canal (IAC) or sella, for example, a thin-layer CT scan is mandatory. Also during surgery of sphenoid wing meningioma with bone involvement or when using the supraorbital approach, a CT scan may be valuable. Preoperatively, the evaluation of several aspects is important:

a. Disposition of the bony labyrinth (vestibule, semicircular canals, and cochlea) before drilling of the IAC and avoiding injury of these structures

b. Disposition and height of the jugular bulb in relation to the posterior wall of the IAC

c. Extension of the pneumatization of the mastoid cells during suboccipital craniotomy and opening of the IAC's posterior wall

d. Location of the emissary vein during suboccipital craniotomy

e. Location of the frontal sinus when using the supraorbital approach

f. Configuration of the sella and sphenoid sinus during surgery of intra-, para-, and suprasellar lesions

g. Extension of bone infiltration by tumors such as sphenoid wing meningioma and others

Preoperative computed tomography angiography (CT-angiography) is useful in some cases, demonstrating tumor blood supply and patency of sinuses, veins, and arteries. Tridimensional representation of aneurysm configuration and its relationship with parent, branching, and perforating arteries is likewise helpful in selected circumstances when conceiving the surgical strategy.

Angiography is losing ground to CT-angiography and magnetic resonance angiography but is still the gold standard image method for aneurysm, arteriovenous malformation, and dural arteriovenous fistula evaluation before surgery.

Cervical spine x-ray should be performed preoperatively to rule out gross deformities depending on the patient positioning chosen. If there is necessity of extreme rotation, flexion, or extension of the head as in the semi-sitting position, for example, a cervical study prior to surgery may avoid major injuries.

Preoperative planning is a very important "part of the surgery." Previous and meticulous study of images to understand the individual anatomy of each patient should be performed. Planning of surgery should start with choosing the best craniotomy site and the optimal trajectory to the desired spot. Reachability and view angle using microscope and different angled endoscopes should be taken into consideration. Recognition of anatomical variations and the neurovascular relationship is important to achieve the surgical goal with minimal

effort and without undesirable surprises. The comprehension of aneurysm configuration or exact tumor extension when analyzing images before surgery reduces intraoperative time and fulfills surgeon and staff.

6. Underlying pathologies and current indications for endoscopic-assisted surgery

There are several situations in skull base surgery in which the use of the endoscope may supplement the traditional microscopic visualization technique. Endoscopy may, in these surgeries, commonly enhance the exposure of the operative field and frequently provide new information for the surgeon [17-22]. In the authors' experience, benefits of this visualization technique are noted especially in cases in which important neurovascular structures constitute a hindrance for the straight-line view of the microscope or in cases with a narrow surgical corridor and "keyhole" approaches (e.g., supraorbital approach, retrosigmoidal approach, etc.). Situations in which it is important to have a lateral view as in lesions invading the IAC, for example, are another interesting indication for this technique. Because of the high definition images delivered and the proximity of the endoscope tip to the region observed, superior exposition of surface texture may help in differentiating some lesions from normal tissue.

6.1. Aneurysm surgery

Surgical clipping is still the most complete treatment alternative for intracranial aneurysms [19, 23, 24]. Aneurysm complete exclusion of the circulation after clipping without occlusion of parent, branching, and perforation vessels is the main goal of the surgical therapy. Large series reported incidences of unexpected residual filling and parent artery occlusion after clipping 4–19% and 0.3–12%, respectively [19, 23]. With the continuous advances in endovascular technologies for the treatment of aneurysms, patients undergoing coiling have increased considerably [25]. Reduction of undesirable and preventable events is essential to support that the surgical technique remains as a reliable treatment alternative [19].

The gold standard examination for evaluation after aneurysm clipping is still the intraoperative digital subtraction angiography (DSA). Routine intraoperative DSA is however not available in most centers [19]. New techniques to better expose and understand the aneurysm anatomy and parent and branching vessels' configuration intraoperatively as the near-infrared indocyanine green video angiography (ICG-VA) and microvascular Doppler sonography (mDs) have been developed. A study in 2010 analyzing both techniques concluded that the methods are complementary and the drawbacks could be compensated by each other. In this report, when both techniques were simultaneously used, 90% of all aneurysms could be correctly evaluated. If only one of these techniques was used, evaluations were correct in about 80% of the cases [23]. These intraoperative techniques have also some weak points. Blood flow assessment in small perforators is not possible using the mDs and illumination deep in the surgical field may be deficient during ICG-VA when small craniotomies are performed [23]. Particularly, because of the straight-line view of the microscope, these techniques have the

limited capacity to expose areas behind vessels or the aneurysm sac. To overcome this situation, a mirror or a high-definition image endoscope may be used.

Endoscopy has several advantages (definition, magnification, etc.) in comparison with a simple micromirror during aneurysm surgery. It has been used in different stages of surgery and presented to be safe and effective diminishing unexpected findings as incomplete aneurysm occlusion or parent vessels' compromise in large series reports [19, 26, 27]. About a lower retraction of the nervous structures and reduced morbidity has also been reported [26].

The decision of whether or not to use the endoscope should be based on the preoperative imaging. If this reveals an intricate anatomy, endoscope set and tower should be prepared for possible application. Intraoperative, insufficient exposure of perforators and/or aneurysm anatomy is an indication for the endoscopic-assisted surgery.

6.2. Cerebellopontine angle

The cerebellopontine angle (CPA) is a complex region of the skull base, with elaborated neurovascular structures and little space. Tumors growing in the CPA tend to disturb cranial nerve functions, brainstem, cerebellum, and eventually cerebrospinal fluid circulation. Different tumors incurring in this location present different behaviors, infiltrating, pushing, or adhering to important structures. Some lesions "create space," pushing structures and sometimes facilitating the approach. Epidermoid tumors, for example, frequently spread around cranial nerves, arteries, and veins invading recesses and corners making complete tumor resection under the straight line view of the microscope difficult, sometimes impossible. Use of endoscopy additionally to the microscope enables a safe removal of such tumors, reduces the extra retraction of nerves and vessels, and eliminates the necessity of enlarging the craniotomy in some cases [22].

The use of the endoscopic-assisted technique during the removal of epidermoid tumors of the posterior fossa is recommended in almost all cases because of the growing behavior of these lesions.

6.2.1. Vestibular Schwannoma

Vestibular schwannomas are benign tumors that generally arise from the vestibular portion of the vestibulocochlear nerve. The region where this tumor grows (Obersteiner–Redlich zone), where the nerve covering myelin changes from central to peripheral type, is close to the opening of the internal auditory canal (IAC) [28]. Dandy considered, in 1941, that surgery of these tumors was the most difficult of all neurosurgical procedures [29]. Resection of these kinds of lesions is still nowadays frequently not easy. One reason for that is the invasion of tumor in the IAC. Visualization of the whole resection area of intrameatal tumors using the microscope is usually just possible after opening the posterior meatus wall. In several cases, the opening of the IAC is not sufficient by risk of damage to the vestibular system and cochlea. By some patients, with high jugular bulb, the complete opening of the IAC is difficult or, sometimes, nearly impossible. Because of the histological benign behavior of this tumor, complete tumor resection with preservation of neurovascular structures and their function is in most cases the aim of surgery.

The capability of the wide view angle of the endoscope associated to the superb illumination of the field enables a deeper exposure of the IAC and eventually residual tumor after resection under microscope view [18, 30-34].

Endoscopy is indicated in cases with deep intrameatal seated vestibular schwannomas, far medial placed labyrinth structures, and high jugular bulb.

6.2.2. Neurovascular compression syndromes

Microvascular decompression (MVD) is an important alternative in the treatment of trigeminal neuralgia and hemifacial spasm. Other neurovascular compression syndromes, such as disabling positional vertigo, tinnitus, and glossopharyngeal neuralgia may also, sometimes, be treated through this surgical option [35]. Several vessels may be responsible for the neurovascular conflict. Arteries and also veins can be compressing the nerve. The neurovascular conflict usually occurs at the root exit or entry zone, but compression of the trigeminal nerve distally in Meckel's cave has been described as well [35].

The incidence of identification of a neurovascular conflict during MVD using the microscope oscillates between 25% and 98% in large series [35-37]. The reason of the inability to recognize a neurovascular conflict could be a negative exploration, as the probability to find the site of nerve compression increases with the surgeon's experience [35, 36]. Insufficient visualization of the root exit zone in Meckel's cave or an incomplete view of the inferior and anterior aspect of the trigeminal nerve were also described as a possible reason for a negative exploration during decompression [35].

The use of endoscopy in MVD surgeries has already been described by some authors in the literature [35, 36, 38, 39]. In these cases, a recognition of 100% of the site of compression was reported [35, 36, 38, 39].

During surgeries of neurovascular compression syndromes, the use of endoscopy is specially indicated in cases with unclear or poor exposure of the neurovascular conflict.

6.3. Intraparenchymal lesions of the brainstem and cerebellum

The neurosurgical approach to deep seated intraparenchymal lesions of the cerebellum and particularly of the brainstem should be kept as small as possible to avoid unnecessary injuries. Because of the balloon-like shape frequently assumed by the resection cavity, the whole operative field view is not always possible using the straight-line view of the microscope. In these cases, an incomplete resection of the lesion with the microscopic vision may occur. Bertalanffy et al. described in 1991 about the increased risk of a secondary hemorrhage after incomplete resection of deep-seated brainstem cavernomas. In this series, residual cavernous hemangioma induced bleeding in two cases [40]. The use of an endoscope may be useful decreasing the deficit of the microscope during the exposure of a cavity though a small opening. This technique can help the surgeon, peculiarly in cases of cavernous hemangiomas and hemangioblastomas. The use of endoscopy should be indicated in cases of deep seated brainstem and cerebellum lesions and by the existence of a small resected cavity.

6.4. Meningioma

Surgery of skull base meningiomas is challenging. The frequently demanding approach, the close relation with important neurovascular structures, and the possible involvement of bone are some of the adversities found during the surgical treatment of this disease. Not rarely, bone, dura mater, vessels, and cranial nerves are superposed to tumor parts and restrict the straight-line view of the microscope [41]. The endoscopic-assisted microsurgery technique is an advantage for skull base meningioma surgery in the hand of experienced surgeons. Use of different angled endoscopes may reduce craniotomy size, skull base drilling, and brain retraction in selected cases [41].

Reasons for employing the endoscope during surgery of skull base meningiomas are the intricate relationship of tumor with neurovascular structures, deep seated lesions, and inadequate exposure of the anatomy because of an insufficient angle of view, small craniotomy, and preoperative images revealing possible blind corners.

7. Treatment

The first step before treatment of a skull base pathology is the individual understanding of the disease, patient's anatomy, and patient's expectations. By means of a careful imaging examination and recognition of the relationship of important anatomical structures, possible pathways and eventual pitfalls as well as the understanding of the clinical presentation and patient's expectation, the decision for the best treatment choices can be made.

Whether or not to use the endoscope initially, during or at the end of surgery for inspection may be determined by the pathology or preoperative image findings. There are different endoscopic-assisted techniques available, and the most appropriate should be chosen depending on the needs of each case. Some of these endoscopic-assisted surgical alternatives for the treatment of skull base pathologies are discussed in the following text.

7.1. Surgical clipping

The endoscopic technique during aneurysm clipping should always be used in combination with the standard microscopic visualization so that benefits of both methods may represent an advantage (Fig. 1). The endoscopic-assisted surgical technique may be used in different situations during aneurysm clipping:

a. Inspection of the aneurysm anatomic and topographical configuration as well as of its surroundings

b. Clipping under endoscopic view, when the approach is limited (e.g., supraorbital keyhole approach)

c. Post-clipping evaluation, checking for complete occlusion, parent vessel, or perforating artery occlusion or restriction [19]

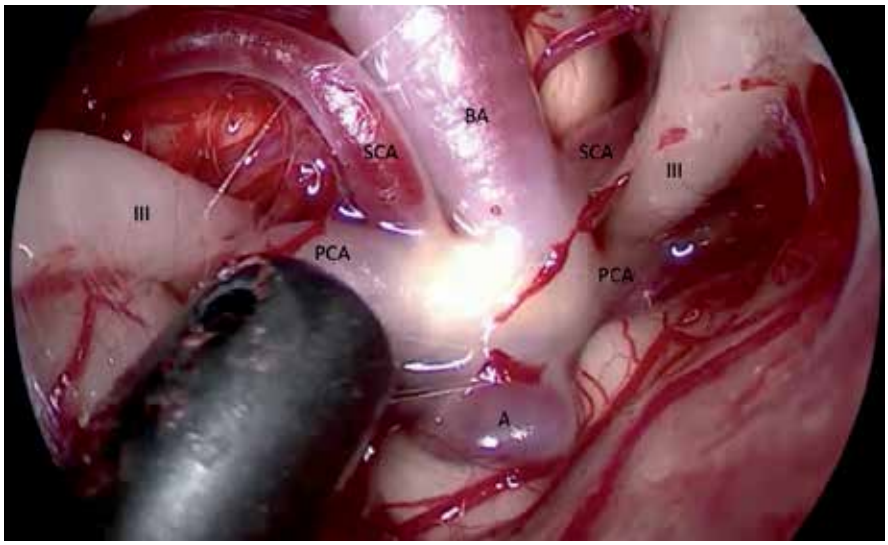

Figure 1. Endoscopic view during inspection of a basilar artery aneurysm before clipping and exposure of the surgical field through the left opto-carotid window and a pterional approach. III, oculomotor nerve; PCA, posterior cerebral artery; SCA, superior cerebellar artery; BA, basilar artery; A, aneurysm sac. (Klinik fuer Neurochirurgie—Universitaet des Saarlandes—Prof. Oertel/Dr. Montibeller)

Use of this technique showed to enhance the completeness of aneurysm occlusion and diminish compromise of involved vessels in a large study series [19].

A novel technique with the endoscopic near-infrared indocyanine green video angiography (ICG-VA) was developed. The aim of this new method is to compensate the weakness of the traditional microscope ICG-VA in the evaluation of vessels located in the depth of the surgical field particularly through small craniotomies. The first results of the comparison of both methods in 40 cases revealed that in 27.5% of cases the endoscopic ICG-VA provided better results for the evaluation of the post-clipping situation. Prevention of neck remnant or branch occlusion could be prevented in four cases, changing the surgical procedure [6].

7.2. Cerebellopontine angle tumor resection

Endoscopy may help in different situations maximizing the exposure of the surgical field during operations in the CPA. The deepness of this region and the complexity of its neuro-vascular anatomy represent an obstacle to the straight-line view of the microscope. Use of the endoscope in the CPA should, also because of that, be performed by experienced hands. We advocate that insertion of the endoscope in the posterior fossa should always be performed under microscopic view. After initial orientation, the surgeon's sight may switch to the endoscopic monitor.

Changes between angled endoscopes should be performed to offer the optimal exposition for different situations. It is very important to pay attention to the direction of the insertion of the endoscope, especially when using angled optics. With the angled view, the direction of

movement is not the same of sight. Depending on the angle of the optic used and the angle of view, the trajectory of positioning may eventually not be seen with the endoscope.

Because of the narrowness of this region, lens blurring is a frequent problem encountered during inspection. To prevent this issue, the suction tip can be held close to the endoscope tip. This reduces the moisture and keeps the lenses dry. Cleaning of lenses with warmed-up water also helps to minimize this undesirable situation.

7.2.1. Intrameatal tumor resection

Endoscopy may be useful during surgery of tumors invading the IAC (Fig. 2). Especially those with a deep extension inside the canal. The endoscope revealed to be helpful finding residual tumor in 11.1–48.1% of selected cases after microscopic resection during vestibular schwannoma surgery [18, 21, 31-34, 42]. An advantage could also be seen during surgery of other tumors invading the IAC [17]. The capability to look further inside the IAC even before opening it in comparison with the microscope has been proven in cadaveric studies [30].

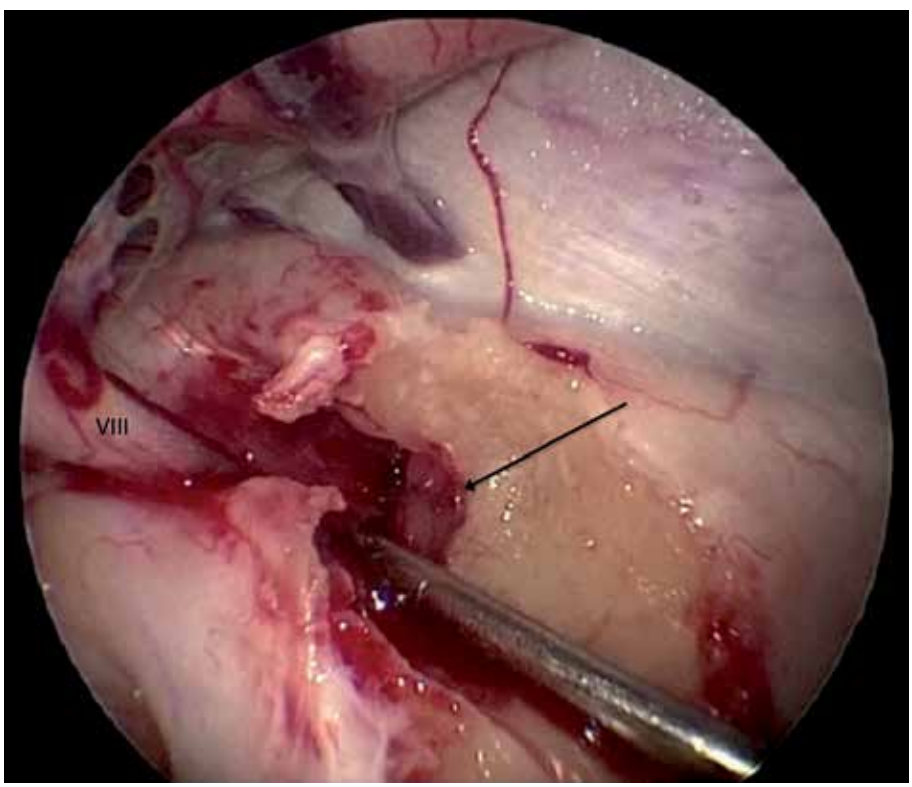

Figure 2. Endoscopic view of the opened internal auditory canal after microscopic resection of a small intrameatal vestibular schwannoma at the right side in semi-sitting position. Detection of intrameatal residual tumor (arrow) due the angled view of the 30° endoscope. VIII, vestibulocochlear nerve. (Klinik fuer Neurochirurgie—Universitaet des Saarlandes—Prof. Oertel/Dr. Montibeller)

The recognition of the facial nerve was facilitated and it could be identified in the early stages of the dissection of vestibular schwannomas using the "look around the corner" technique [32].

Identification of opened air cells minimizing the chance for postoperative cerebrospinal fluid fistula may be another advantage of the endoscopic-assisted technique [31, 43].

Because of the extended view delivered through endoscopy, drilling of the posterior wall of the IAC in cases of a medially placed labyrinth or high jugular bulb may be reduced [30, 44].

7.3. Microvascular decompression

The advantages of the endoscopic-assisted technique during MVD have been described by many authors [17, 35, 36, 38, 39]. The endoscope may be used to inspect the trigeminal and facial nerve root as well as Meckel's cave. This technique may help to identify the compression site, find multiple spots of neurovascular contact, and confirm decompression at the end of surgery [17].

Fully endoscopic MVD has also been described with good results [45].

7.4. Anterior fossa tumor resection

By surgery of tumors of the anterior cranial fossa, the endoscope may also be useful during inspection before and after microscopic resection. Especially in cases of olfactory groove meningiomas, endoscopy may play a role accessing the integrity of the olfactory nerve.

7.5. Intraparenchymal lesions of the brainstem and cerebellum

Introduction of the endoscope inside small resection cavities of brainstem or cerebellum may provide an advantage for the inspection of the whole wall of the cavity and rule out bleeding spots or residual tumor after microscopic resection.

8. Endoscopic setting

Special microsurgical instruments and technique are necessary as well as microsurgical experience. Changing the views between microscope and endoscope requires attention of the surgeon and his assistant. Several modalities of observing the endoscopic and microscopic images at the same time have been described [4]. Alternating between oculars of microscope and the video screen of the endoscopy, numerous variations may be possible. We use the oculars of the microscope for the microscopic image and a video screen placed in front of the surgeon to display the endoscopic image (Fig. 3). The position of equipment and staff in the operating room is very important so that the surgeon is able to move in an ergonomic or user-friendly way maximizing his coordination. An example with a possible distribution is seen in Fig. 4.

http://dx.doi.org/10.5772/60588

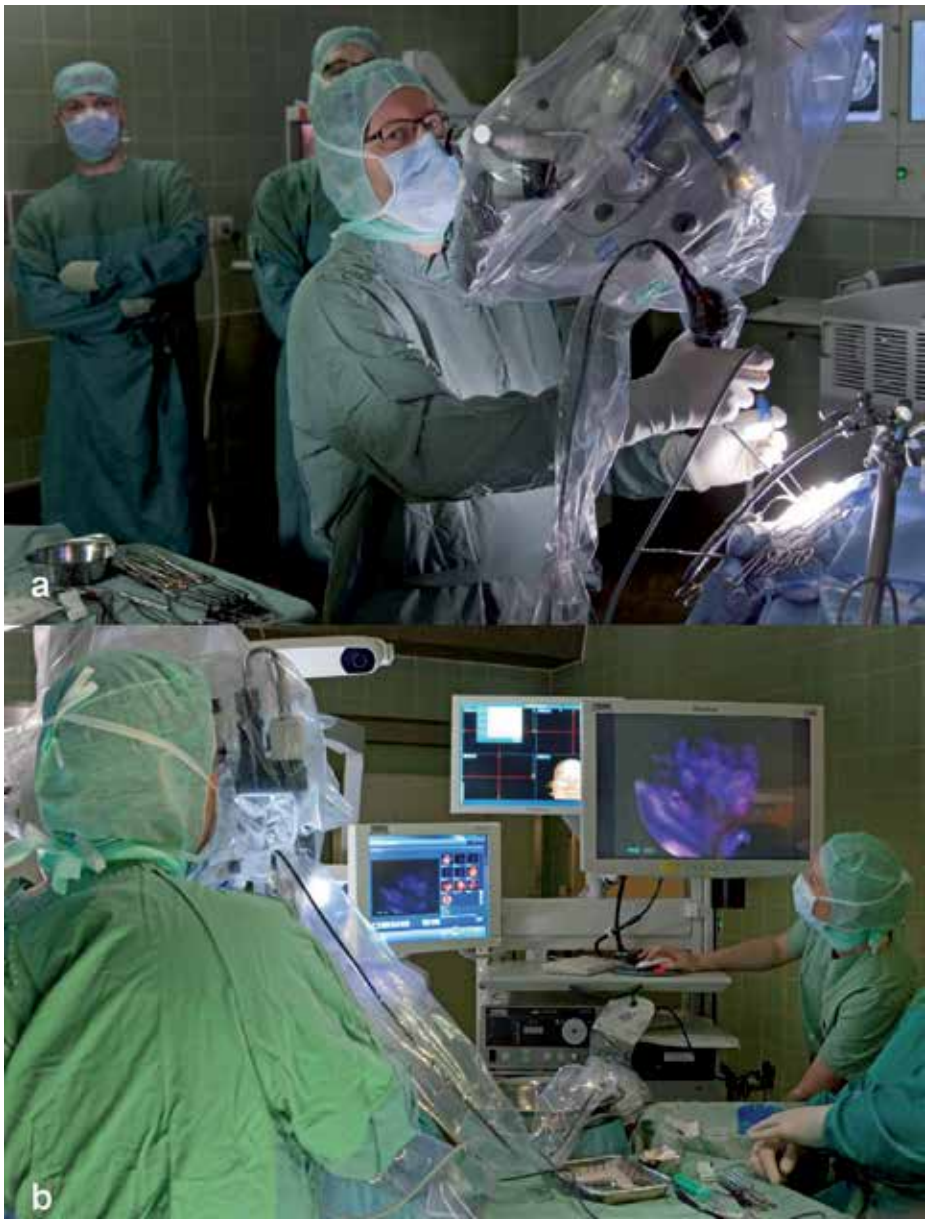

Figure 3. Endoscopic-assisted technique showing the introduction of the endoscope in the surgical field by the surgeon under microscopic view (a) and the position of the endoscope screen (b). (Klinik fuer Neurochirurgie—Universitaet des Saarlandes—photograph of the department: Ruediger Koop)

9. Advantages of endoscopic-assisted surgery

Neuroendoscopy may offer several advantages in selected cases of skull base surgery in comparison with the microscope. The better illumination of the field due to the proximity of

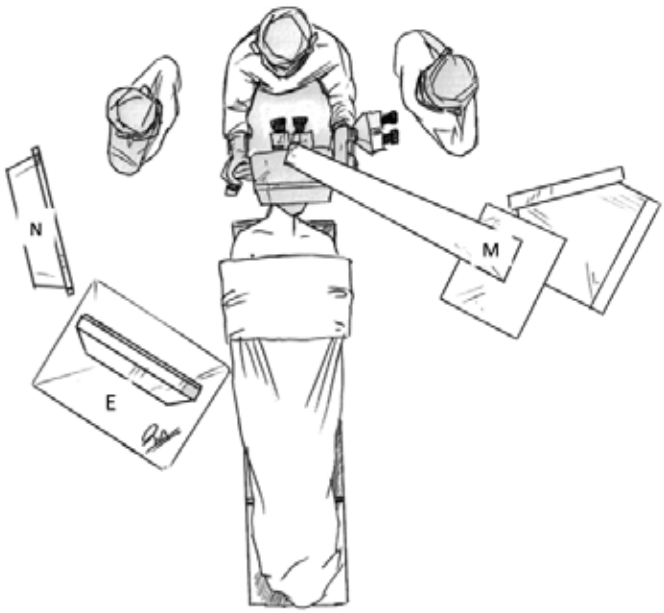

Figure 4. Possible distribution of equipment in the operation theatre providing a user-friendly movement of the surgeon. M: microscope, E: endoscope screen, N: neuronavigation screen. (Dr. Erasmo Barros da Silva Junior)

the endoscope tip to the tissue and the high definition images delivered by the new generation equipment offer an excellent visualization of the surgical field. Also, the different perception of tissue texture is observed when both techniques are compared. The expanded view angle and different possible "looks" using a movable instrument is of course also a benefit in some skull base surgeries with a complex anatomy. Reduced tissue mobilization and the necessity of retraction of important structures as well as reduced trauma are a consequence of the different view angle capability of the neuroendoscope when compared with the microscope. Finding additional information at target in some skull base surgeries is obviously a great benefit of the endoscopy. In the authors' experience, most of this technique during skull base surgery in the actual days may be achieved when using both techniques, microscope and neuroendoscope, together as supplementary and additive devices.

10. Disadvantages of endoscopic-assisted surgery

Some disadvantages of the endoscope when compared with the image delivered by the microscope are as follows:

a. Inferior 3D-perception of the images. Compensated with surgeon's experience time but cannot be set side by side with the microscope, at least not with the current technology. New 3D-endoscopes are in development and trying to improve this issue.

b. Distortion of images is another issue that should be considered a disadvantage of the endoscopic images. Especially in deep areas, images get deformed in size. Angled endoscopes also distort the images that are distant from the tip [30].

c. Time consuming — Gerganov et al. analyzed the additional time for the use of this technique during the removal of vestibular schwannomas and concluded that 15–20 minutes extra time was needed in the operating theater applying the endoscope [13]. We believe it is very difficult to exactly calculate the additional time needed for the use of this technique. Some information given through endoscopy may even shorten the operative time. Particularly, only one case with complete tumor removal instead of leaving remnant tumor behind will justify any additional surgical time. If the endoscopic equipment is prepared and set in standby in every skull base surgery, undesirable waste of time may be avoided.

11. Complications and risks

Some authors also reported about the complications and limitations of this technique [22, 34, 41, 46, 47]. The use of endoscopy during skull surgery may correlate with iatrogenic damage of nerves and vessels [46]. Hori et al. reported about the injury of the facial nerve during inspection with the endoscope in one case of a series [34].

The risk of using this instrument, especially with the 30°, 45°, and 70° angulated optics should be kept in mind. With angulated scopes, it is not always easy to know where the tip of the instrument is and the introduction of this tool in the operative field should be performed under microscopic view.

12. Conclusions

Vestibular schwannomas, trigeminal schwannomas, epidermoid tumors, hemifacial spasms, cerebellopontine angle meningiomas, anterior fossa meningiomas, and aneurysms between others are some of the skull base pathologies with which the endoscope can be helpful giving some additional information on the target. The neuroendoscope is usually used for inspection of the situs and not as the main source for imaging. In a few selected circumstances, endoscopic-assisted surgery present a benefit in comparison with the microscope and can be used during the preparation of structures, resection of tumors (e.g., intrameatal vestibular schwannoma or epidermoid tumor), or clipping intricate aneurysms.

Endoscopy in microsurgical removal of vestibular schwannomas may be useful, especially in cases with small deep intrameatal tumors and of high-positioned jugular bulb. Inspection of the fundus of the internal auditory canal may permit the identification of eventual remnant tumor.

In epidermoid tumors, endoscopic inspection, and endoscopic-assisted tumor resection are of great value, particularly in the posterior fossa, finding remnant tumor and reaching difficult

and delicate areas. In epidermoid tumor surgery of the cerebellopontine angle, when remnants are not visible in a straight line, the endoscope-assisted technique can contribute to safe tumor removal. It also allows the resection of tumor extensions without retracting neurovascular structures or enlarging the craniotomy.

In trigeminal neuralgia, the endoscope may help when the neurovascular conflict cannot be identified using the straight-line view of the microscope.

In aneurysm surgery, endoscopy is especially useful in deep-seated lesions and in aneurysms with suspicion of perforators on their backside. In some cases, additional information on aneurysm occlusion and on the patency of parent, branching, and perforating arteries can be gained.

The possibility of introduction of the tip of the endoscope into deep areas and the use of different angle scopes widening the field of view permit the reduction of surgical trauma during the approach, by reduced retraction of structures. Discovery of additional information at target, however, is certainly the principal advantage of this tool. Novel indications for endoscopy in the skull base surgery are growing fast and different uses of this device are being tested.

Acknowledgements

The authors thank Mr. Ruediger Koop for the nice pictures exposing the real surgical situations using the endoscopic-assisted technique and Dr. Erasmo Barros da Silva Junior for his attractive illustration of the ergonomic equipment distribution in the operating room.

Joachim Oertel acts as consultant for Karl Storz Company. Thank you for your cooperation!

Author details

Joachim M.K. Oertel* and Guilherme Ramina Montibeller

*Address all correspondence to: oertelj@freenet.de

Saarland University Medical Center, Homburg, Germany

References

[1] Grunert P, Gaab MR, Hellwig D, Oertel JM. German neuroendoscopy above the skull base. Neurosurgical focus. 2009;27(3):E7.

[2] Grunert P, Oertel J. Technical and clinical evolution of modern neuroendoscopy. In: Iancu C, editor. Advances in Endoscopic Surgery: InTech; 2011. p. 175-90.

[3] Morcos JJ. Editorial: endoscopy and skull base. Journal of neurosurgery. 2012;117(4): 687-9.

[4] Perneczky A, Fries G. Endoscope-assisted brain surgery: part 1--evolution, basic concept, and current technique. Neurosurgery. 1998;42(2):219-24; discussion 24-5.

[5] Epstein M. Endoscopy: developments in optical instrumentation. Science. 1980;210(4467):280-5.

[6] Rediker J, Fischer G, Oertel J. Endoscope- vs. microscope-integrated near-infrared indocyanine green videoangiography (ICG-VA) in aneurysm surgery. Abstractband 65 Jahrestagung der Deutschen Gesellschaft für Neurochirurgie (DGNC); 13-16.06.20122014.

[7] Ebner FH, Marquardt JS, Hirt B, Tatagiba M, Schuhmann MU. Visualization of the anterior cerebral artery complex with a continuously variable-view rigid endoscope: new options in aneurysm surgery. Neurosurgery. 2010;67(2 Suppl Operative):321-4.

[8] Ebner FH, Marquardt JS, Hirt B, Feigl GC, Tatagiba M, Schuhmann MU. Broadening horizons of neuroendoscopy with a variable-view rigid endoscope: an anatomical study. European Journal of Surgical Oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2010;36(2): 195-200.

[9] Donald PJ. History of skull base surgery. Skull Base Surgery. 1991;1(1):1-3.

[10] Ojemann RG. Skull-base surgery: a perspective. Journal of Neurosurgery. 1992;76(4): 569-70.

[11] Ramina R, Aguiar PHPd, Tatagiba M. Samii's Essentials in Neurosurgery. Berlin Heidelberg, Germany: Springer-Verlag; 2014.

[12] Tatagiba M, Acioly MA. Vestibular Schwannoma: Current State of the Art. In: Ramina R, Aguiar PHPd, Tatagiba M, editors. Samii's Essentials in Neurosurgery. Berlin Heidelberg, Germany: Springer-Verlag; 2014. p. 265-83.

[13] Roser F, Ebner F. Sphenoid Wing Meningiomas. In: Ramina R, Aguiar PHPd, Tatagiba M, editors. Samii's Essentials in Neurosurgery. Berlin Heidelberg, Germany: Springer-Verlag; 2014. p. 173-83.

[14] Matthies C. Functional Microsurgery of Vestibular Schwannomas. In: Ramina R, Aguiar PHPd, Tatagiba M, editors. Samii's Essentials in Neurosurgery. Berlin Heidelberg, Germany: Springer-Verlag; 2014. p. 285-300.

[15] Yeom KW, Lober RM, Mobley BC, Harsh G, Vogel H, Allagio R, et al. Diffusion-weighted MRI: distinction of skull base chordoma from chondrosarcoma. AJNR American Journal of Neuroradiology. 2013;34(5):1056-61, S1.

[16] Parizel PM, Hauwe LVD, Belder FD, Goethem JV, Venstermans C, Salgado R, et al. Magnetic Resonance Imaging of the Brain. In: Reimer P, Parizel PM, Meaney JFM, Stichnoth F-A, editors. Clinical MR Imaging, A Practical Approach; 2010.

[17] Montibeller GR, Oertel J. Endoskopisch assistierte Operationen der hinteren Schädelgrube. Abstractband "Hintere Schädelgrube und kraniozervikaler Übergang - innovative Techniken" 30-30-21 Jahrestagung der Gesellschaft für Schädelbasischirurgie e V (GSB); Tübingen, Germany; 2013.

[18] Montibeller GR, Gaab MR, Oertel J. What is the role of the endoscope during microsurgical removal of vestibular schwannomas? Abstractband 63 Jahrestagung der Deutschen Gesellschaft für Neurochirurgie (DGNC); 13-16.06.20122012.

[19] Fischer G, Oertel J, Perneczky A. Endoscopy in aneurysm surgery. Neurosurgery. 2012;70(2 Suppl Operative):184-90; discussion 90-1.

[20] Tuchman A, Platt A, Winer J, Pham M, Giannotta S, Zada G. Endoscopic-assisted resection of intracranial epidermoid tumors. World neurosurgery. 2013.

[21] Kumon Y, Kohno S, Ohue S, Watanabe H, Inoue A, Iwata S, et al. Usefulness of endoscope-assisted microsurgery for removal of vestibular schwannomas. Journal of Neurological Surgery Part B, Skull Base. 2012;73(1):42-7.

[22] Schroeder HW, Oertel J, Gaab MR. Endoscope-assisted microsurgical resection of epidermoid tumors of the cerebellopontine angle. Journal of Neurosurgery. 2004;101(2): 227-32.

[23] Fischer G, Stadie A, Oertel JM. Near-infrared indocyanine green videoangiography versus microvascular Doppler sonography in aneurysm surgery. Acta Neurochirurgica. 2010;152(9):1519-25.

[24] David CA, Vishteh AG, Spetzler RF, Lemole M, Lawton MT, Partovi S. Late angiographic follow-up review of surgically treated aneurysms. Journal of Neurosurgery. 1999;91(3):396-401.

[25] Nakamura M, Montibeller GR, Gotz F, Krauss JK. Microsurgical clipping of previously coiled intracranial aneurysms. Clinical Neurology and Neurosurgery. 2013;115(8):1343-9.

[26] Perneczky A, Boecher-Schwarz HG. Endoscope-assisted microsurgery for cerebral aneurysms. Neurologia Medico-Chirurgica. 1998;38 Suppl:33-4.

[27] Kalavakonda C, Sekhar LN, Ramachandran P, Hechl P. Endoscope-assisted microsurgery for intracranial aneurysms. Neurosurgery. 2002;51(5):1119-26; discussion 26-7.

[28] Betka J, Chovanec M, Zverina E, Profant O, Lukes P, Skrivan J, et al. Minimally Invasive Endoscopic and Endoscopy-Assisted Microsurgery of Vestibular Schwannoma. In: Iancu C, editor. Advances in Endoscopic Surgery: InTech; 2011.

[29] Ramina R, Aguiar PH, Tatagiba M. Samii's Essentials in Neurosurgery: Springer; 2007.

[30] Montibeller GR, Fries F, Petrakakis I, Becker KW, Oertel J. Comparison of microscopic and endoscopic view of the internal auditory canal - A cadaveric study. Abstractband 65 Jahrestagung der Deutschen Gesellschaft für Neurochirurgie (DGNC); 13-16.06.20122014.

[31] Wackym PA, King WA, Poe DS, Meyer GA, Ojemann RG, Barker FG, et al. Adjunctive use of endoscopy during acoustic neuroma surgery. The Laryngoscope. 1999;109(8):1193-201.

[32] Gerganov VM, Romansky KV, Bussarsky VA, Noutchev LT, Iliev IN. Endoscope-assisted microsurgery of large vestibular schwannomas. Minimally Invasive Neurosurgery : MIN. 2005;48(1):39-43.

[33] Chovanec M, Zverina E, Profant O, Skrivan J, Cakrt O, Lisy J, et al. Impact of videoendoscopy on the results of retrosigmoid-transmeatal microsurgery of vestibular schwannoma: prospective study. European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies. 2013;270(4):1277-84.

[34] Hori T, Okada Y, Maruyama T, Chernov M, Attia W. Endoscope-controlled removal of intrameatal vestibular schwannomas. Minimally Invasive Neurosurgery : MIN. 2006;49(1):25-9.

[35] Rak R, Sekhar LN, Stimac D, Hechl P. Endoscope-assisted microsurgery for microvascular compression syndromes. Neurosurgery. 2004;54(4):876-81; discussion 81-3.

[36] Badr-El-Dine M, El-Garem HF, Talaat AM, Magnan J. Endoscopically assisted minimally invasive microvascular decompression of hemifacial spasm. Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2002;23(2):122-8.

[37] Papanagiotou P, Grunwald IQ, Politi M, Struffert T, Ahlhelm F, Reith W. [Vascular anomalies of the cerebellopontine angle]. Der Radiologe. 2006;46(3):216-22.

[38] King WA, Wackym PA, Sen C, Meyer GA, Shiau J, Deutsch H. Adjunctive use of endoscopy during posterior fossa surgery to treat cranial neuropathies. Neurosurgery. 2001;49(1):108-15; discussion 15-6.

[39] Charalampaki P, Kafadar AM, Grunert P, Ayyad A, Perneczky A. Vascular decompression of trigeminal and facial nerves in the posterior fossa under endoscope-assisted keyhole conditions. Skull base : Official Journal of North American Skull Base Society [et al]. 2008;18(2):117-28.

[40] Bertalanffy H, Gilsbach JM, Eggert HR, Seeger W. Microsurgery of deep-seated cavernous angiomas: report of 26 cases. Acta Neurochirurgica. 1991;108(3-4):91-9.

[41] Schroeder HW, Hickmann AK, Baldauf J. Endoscope-assisted microsurgical resection of skull base meningiomas. Neurosurgical Review. 2011;34(4):441-55.

[42] King WA, Wackym PA. Endoscope-assisted surgery for acoustic neuromas (vestibular schwannomas): early experience using the rigid Hopkins telescope. Neurosurgery. 1999;44(5):1095-100; discussion 100-2.

[43] Valtonen HJ, Poe DS, Heilman CB, Tarlov EC. Endoscopically assisted prevention of cerebrospinal fluid leak in suboccipital acoustic neuroma surgery. The American Journal of Otology. 1997;18(3):381-5.

[44] Pillai P, Sammet S, Ammirati M. Image-guided, endoscopic-assisted drilling and exposure of the whole length of the internal auditory canal and its fundus with preservation of the integrity of the labyrinth using a retrosigmoid approach: a laboratory investigation. Neurosurgery. 2009;65(6 Suppl):53-9; discussion 9.

[45] Lang SS, Chen HI, Lee JY. Endoscopic microvascular decompression: a stepwise operative technique. ORL; Journal for Oto-Rhino-Laryngology and Its Related Specialties. 2012;74(6):293-8.

[46] Gerganov VM, Giordano M, Herold C, Samii A, Samii M. An electrophysiological study on the safety of the endoscope-assisted microsurgical removal of vestibular schwannomas. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2010;36(4):422-7.

[47] Tatagiba M, Matthies C, Samii M. Microendoscopy of the internal auditory canal in vestibular schwannoma surgery. Neurosurgery. 1996;38(4):737-40.

Chapter 15

New Frontiers in Managing Clival Tumors — The Extended Endoscopic Endonasal Approach

G. Cossu, R.T. Daniel, M. George, F. Parker, N. Aghakhani, M. Levivier and M. Messerer

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60553

Abstract

Clival lesions still represent a challenge for neurosurgeons. A variety of expansive process, either benign or malignant, may be identified in the clival and paraclival region.

Surgery of this region with classical open approaches is associated with a significant rate of complication, and the treatment is risky despite technological progress. The acceptance and utilization of endoscopic techniques on a regular basis in transsphenoidal surgery have allowed its application to regions far beyond the *sella turcica*, such as to reach the clival and paraclival region.

Long-term follow-up studies show how the extent of oncological resection is related to long-term prognosis for the most common clival malignancies. Gross total removal is therefore mandatory, and the selection of the best surgical approach is essential for the achievement of this goal.

The choice of the surgical approach depends on the location and the extent of the lesion. Through a complete overview of surgical anatomy, we propose a surgical classification with three corridors in the sagittal plane and three zones in the coronal plane. We finally summarize the indications and the limits for the endoscopic technique. In selected cases, endoscopic approaches allow similar oncological outcomes as classical open approaches with a lower rate of complications.

Keywords: Clival tumors, Clival chordoma, Clival chondrosarcoma, Meningioma, Extended endoscopic endonasal approach, Skull base surgery

1. Introduction

The clival region may be involved in a copious number of disorders. The most common clival lesions are chordomas, but meningiomas, chondroma and chondrosarcoma may also occur. Furthermore, the clivus may be secondarily invaded by a variety of metastatic malignancies. A radical excision is related to long-term prognosis and survival and a gross total resection is the *primum movens* of every surgical procedure when judged possible. The deep location and the presence of important neurovascular structures make of the clivus a challenging working area. Surgery of this region through classical open approaches implies neurovascular and cerebral retraction with a significant rate of neurological morbidities. Neurosurgeons have thus progressively searched for innovative ways to reach the clival region and to limit the complication rate.

Endoscopy started to be used as a diagnostic tool [1, 2] and then developed as a therapeutic option for sellar lesions [3, 4]. During the last decades, endoscopic techniques were applied to the skull base with encouraging results in terms of surgical resection and rate of complications [5]. Clear advantages of endoscopic surgery are principally a limited retraction on neurovascular structures with a concomitant wide vision and large exposure. Furthermore, patients have no external marks, and the length of hospitalization is normally shorter than with open procedures.

According to their location and extension, clival tumors may be reached through an anterior approach, as extended subfrontal, Le Fort I, transoral approach or maxillotomy, or through a lateral approach as the transpterygoid or infratemporal craniotomy or as the transpetrosal or far lateral approach. The endoscopic technique may represent a valid alternative to these open approaches, and the aim of this chapter is to expose the expanded endoscopic approach as first-line treatment in well-selected patients.

2. Preoperative evaluation

A satisfying preoperative evaluation implies T1 and T2-weighted MRI sequences, with and without gadolinium administration, to evaluate the extent and the precise localization of the lesion in the axial, coronal and sagittal plane. A high-resolution skull base CT scan with bone windows will help to plane the surgical approach and to evaluate bone invasion and osseous pneumatization. A CT angiography will then help to characterize vessels' characteristics, in particular of the ICA, and their reciprocal relationship with the lesion, thus defining the extent of resection. A 3D-scannographic reconstruction may better help understanding the real surgical anatomy of the ventral skull base, with a particular concern for the location of foramen lacerum and vidian canal. Patients should also have an ENT evaluation with a specialized neuro-otological examination and undergo a preoperative endonasal endoscopy to plan the access for the surgery.

http://dx.doi.org/10.5772/60553

3. Surgical procedure

3.1. Surgical anatomy and classification of the surgical approach

The clivus separates the nasopharynx from the posterior cranial fossa and a natural access is possible through the nasal cavities.

From a purely anatomical point of view, the clivus is traditionally divided into basisphenoid (sphenoid body) and basiocciput (basilar part of the occipital bone) (Figure 1).

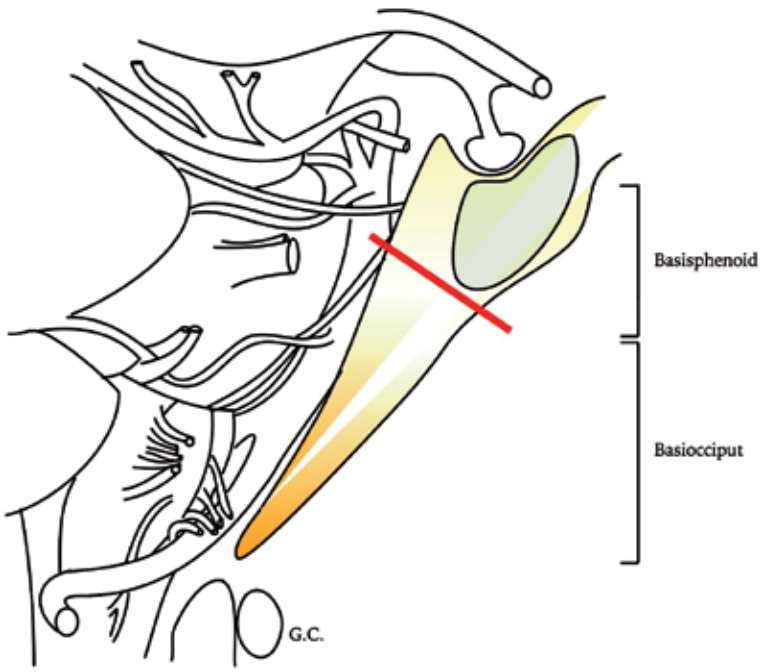

Figure 1. Anatomical classification of the clivus, which is divided into basisphenoid and basiocciput. Classically the sphenoid body forms the basisphenoid while the basiocciput belongs to the occipital bone.

From a surgical point of view, the clivus has classically been divided into [6] (Figure 2):

- an upper clivus extending from the dorsum sellae to the plane of Dorello canal;
- a middle clivus extending from the Dorello canal to the pars nervosa of the jugular foramen;
- a lower clivus extending from the pars nervosa of the jugular foramen to the foramen magnum.

The choice of the surgical approach depends on the location and extension of the lesion, which are the principal determinants for the extent of bone removal. The relationship between the lesion and the pneumatization of the sphenoidal sinus represents the basis of our surgical classification proposed here.

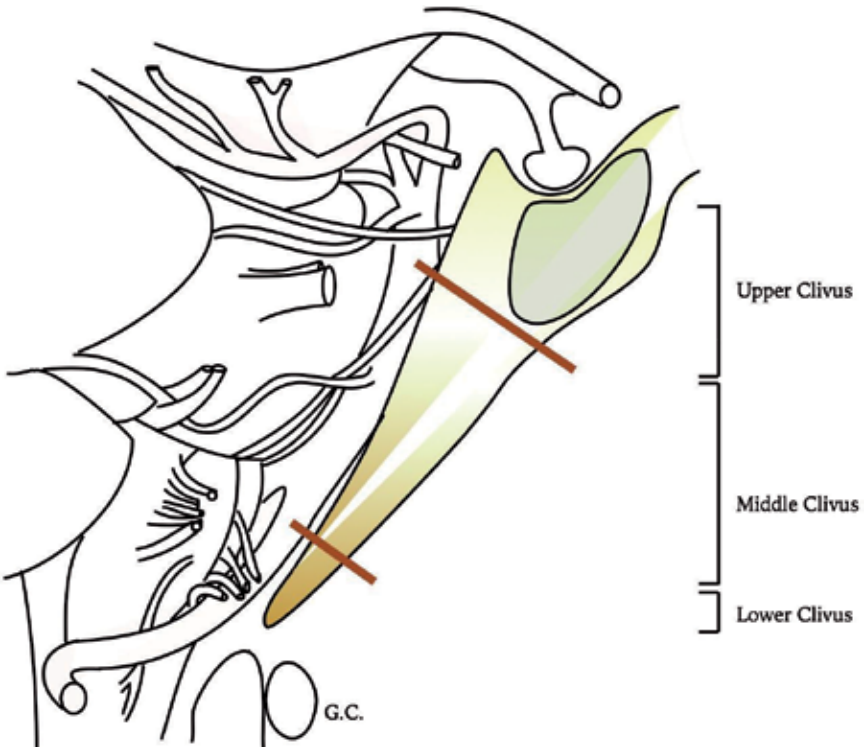

Figure 2. Surgical classification of the clivus. The upper third extends from the dorsum sellae to the Dorello canal. The middle third extends inferiorly till the jugular foramen, while the inferior third extends to the foramen magnum.

Three corridors may be identified in the sagittal plane, separated by two lines (Figure 3). The superior line joins the nostril with the sellar floor, while the inferior line joins the nostril with the inferior wall of the sphenoidal sinus. The superior line separates the trans-sellar corridor, used for lesions of the anterior cranial base and extending till the posterior clinoid process, and the sphenoidal corridor, where the natural pneumatization allows a direct access to the sellar and retrosellar region without the necessity to transpose the pituitary gland as in the trans-sellar corridor [7] (Figure 4). In front of a well-pneumatized sphenoid sinus, the sphenoidal corridor gives an excellent access to mid-clival lesions. The inferior line separates the sphenoidal corridor from the infra-sphenoidal corridor, used to access to the lower part of the clivus after the lateralization of the *longus capitis* and *longus colli* muscles. The identification of the foramen magnum and hypoglossal canals is fundamental to safely use this corridor. A different inclination of the endoscope in the sagittal plane combined with a more or less pronounced flexion or extension of the head of the patient allows direct access to one of the three corridors.

According to our endoscopic conception, three zones are also identified in the coronal plane: the median, paramedian and lateral zone (Figure 5). The medial line, extending from the medial wall of the cavernous sinus to the medial border of the foramen lacerum, separates the median from the paramedian zone. The lateral line, extending from the lateral wall of the

http://dx.doi.org/10.5772/60553

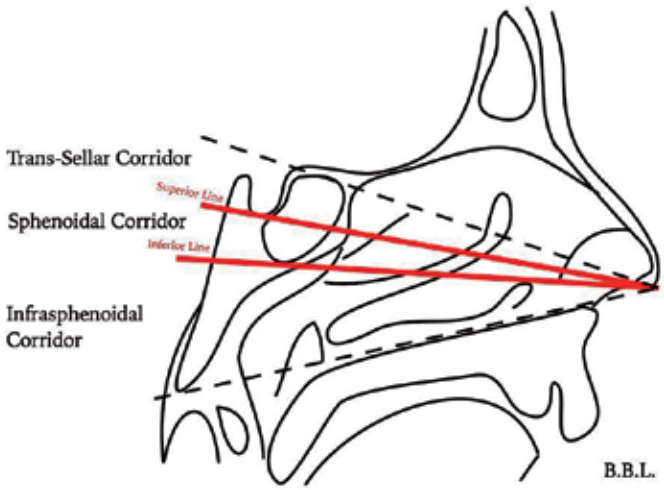

Figure 3. Sagittal view showing the three surgical corridors: the trans-sellar, the sphenoidal and the infra-sphenoidal corridors. The corridor must be chosen on the basis of the location of the lesion. Head flexion and the use of angulated endoscope may help in performing the procedure.

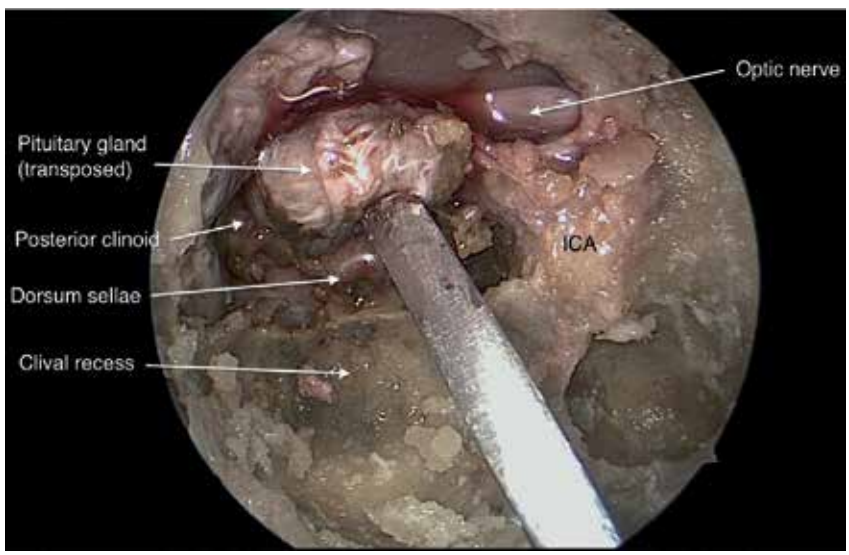

Figure 4. Cadaveric view of a trans-sellar corridor. The pituitary is transposed to drill out the posterior clinoids and the dorsum sellae. The posterior ethmoidal cells are also opened and the left optic nerve is here exposed.

cavernous sinus to the lateral edge of the foramen lacerum, separates the paramedian zone from the lateral zone.

To work safely in the paramedian zone, the identification of the vidian nerve and of the ICA is fundamental [8]. Lesions limited to the median and paramedian zones may be completely

excised through an endoscopic approach, while for lesions extending to the lateral zone a pterygoid or infratemporal craniotomy may be preferred or combined with endoscopy.

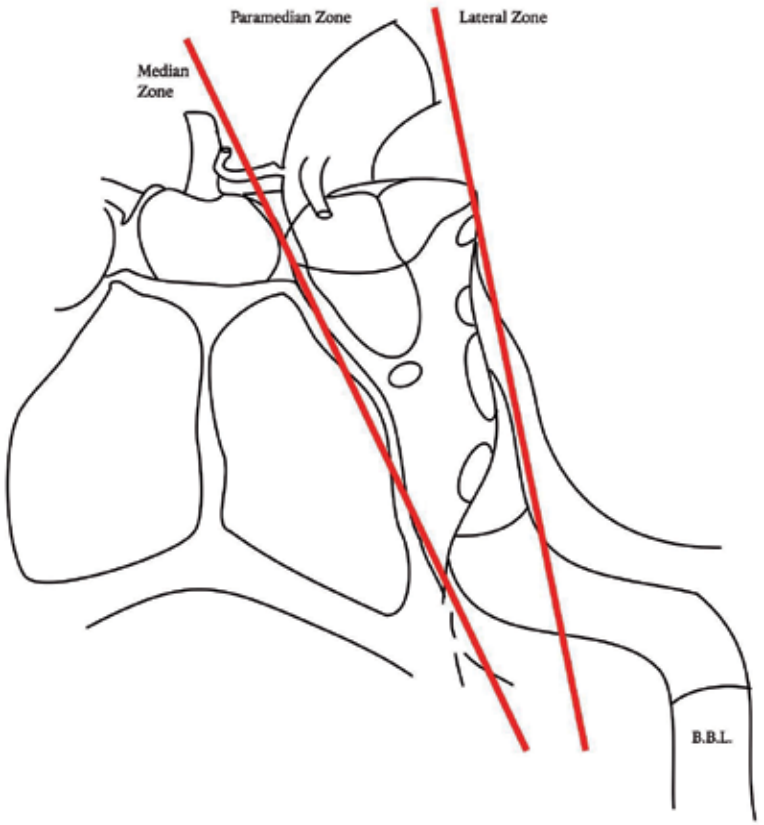

Figure 5. Coronal representation of the three coronal zones. The cavernous sinus and the foramen lacerum represent two important landmarks. A lesion situated solely in the median or paramedian zone may be completely resected through an endoscopic approach. For lesions extending to the lateral zone a combined approach must be considered.

3.2. Operative technique

In most centers, an interdisciplinary team consisting of a neurosurgeon and an otolaryngologist performs the surgery. The patient is positioned supine with the head elevated of 30° and slightly hyperextended. A general anesthesia is performed with an orotracheal intubation. As nerves retraction represent one of the main risk, intraoperative neuromonitoring is performed, allowing direct monitoring of cranial nerve function. Direct stimulation through a monopolar device is commonly used, with a frequency of 1Hz, a monophasic negative 200 μs duration and a 1 to 5 mA intensity stimulation. Eyeball movements are thus monitored through electrodes capturing the displacement of the retina dipole to evaluate the integrity of oculomotor, trochlear and abducens nerves. The frontalis, orbicularis oculi, orbicularis ori and

http://dx.doi.org/10.5772/60553

mentalis muscles are evaluated to monitor the functionality of the facial nerve. Electrodes incorporated in the endotracheal tube (Xomed®) are used for glossopharyngeal and vagus nerves while electrodes in trapezius and hypoglossal muscles are used to monitor accessory-spinal and hypoglossal nerves respectively. Somatosensory evoked potentials and brain stem auditory potentials are also used as complement for brainstem function assessment.

Some centers guide their extent of resection with a neuronavigation system and a Doppler ultrasonography to better visualize adjacent vascular structures as the sphenopalatine artery, the ICA and the basilar artery.

A binostral approach is used according to the four-hand technique *(Figure 6)*. The procedure is performed with a hand-held short 0°, 30° or 45° endoscope till the sellar floor opening. The endoscope is classically first introduced from the right nostril unless the preoperative endonasal evaluation showed a preferential way in the left nostril. The endoscope is oriented slightly rostrally to better visualize the clivus and normally handled in the nostril contralateral to the lesion during the operative procedure.

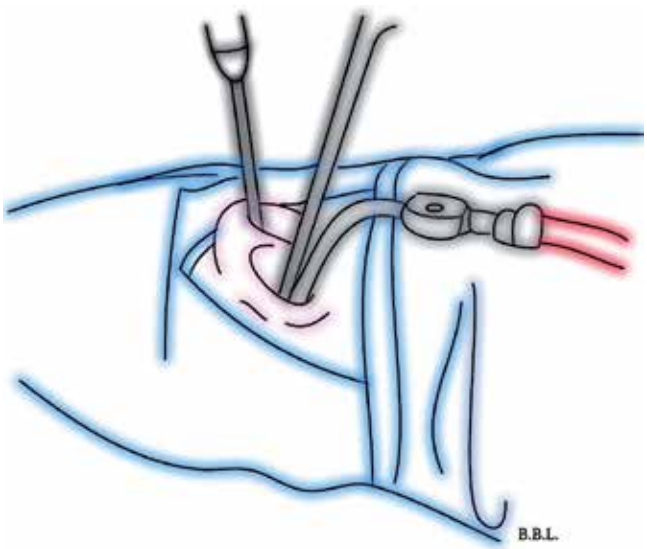

Figure 6. Representation of the *four-hand technique*. The endoscopic is kept by the operative aid in the nostril contralateral to the lesion, while the surgeon freely operates with both hands in the other nostril. This technique implies the presence of two well-trained operators and a strong collaboration between the two surgeons.

Through the endonasal approach, the inferior turbinate is encountered first, then the medial and the superior one, which may be resected or just retracted (Figure 7). To obtain a wider surgical corridor, a resection of the middle and superior turbinates is preferred for extended endoscopic approaches [9, 10, 11, 12, 13] (Figure 8 and 9). Turbinectomies allows also a better visualization of branches of the sphenopalatine arteries, important to preserve for the closure stage.

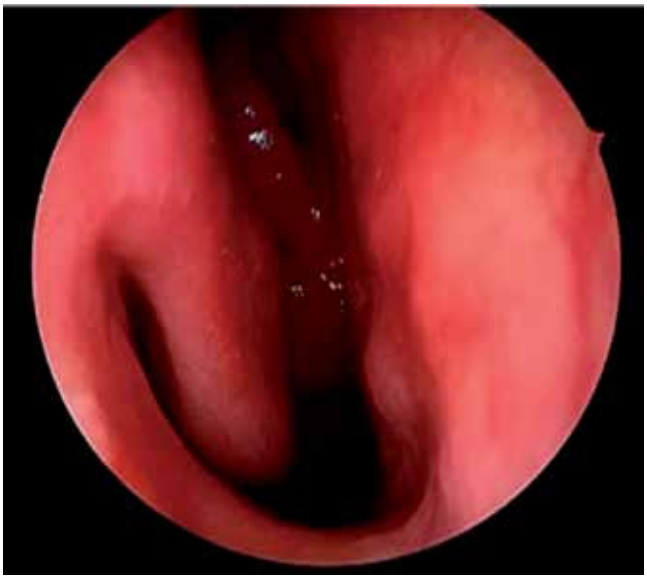

Figure 7. *In vivo* visualisation of the right nasal cavity through a 0° endoscope. At the beginning of the endonasal approach the inferior turbinate is first visualized (left). More deeply the middle turbinate is identified and laterally displaced or resected to gain a wider access to the clival region.

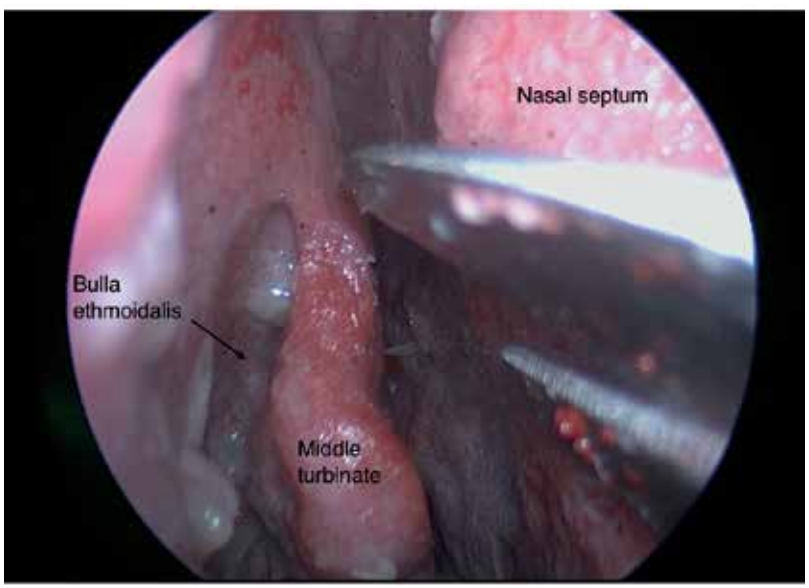

Figure 8. Cadaveric view of the right nasal fossa. The middle turbinate is visualized as well as the bulla ethmoidalis in the lateral wall of the nasal cavity.

The coanes and the inferior wall of the sphenoid sinus are identified.

http://dx.doi.org/10.5772/60553

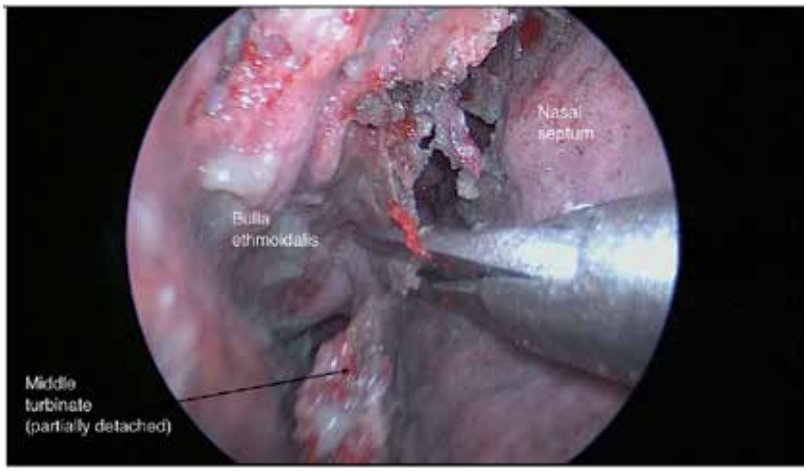

Figure 9. A middle turbinectomy is performed in a cadaveric specimen. A wider endonasal access is thus obtained for more extended approaches. The middle turbinate may then be used during the closure stage.

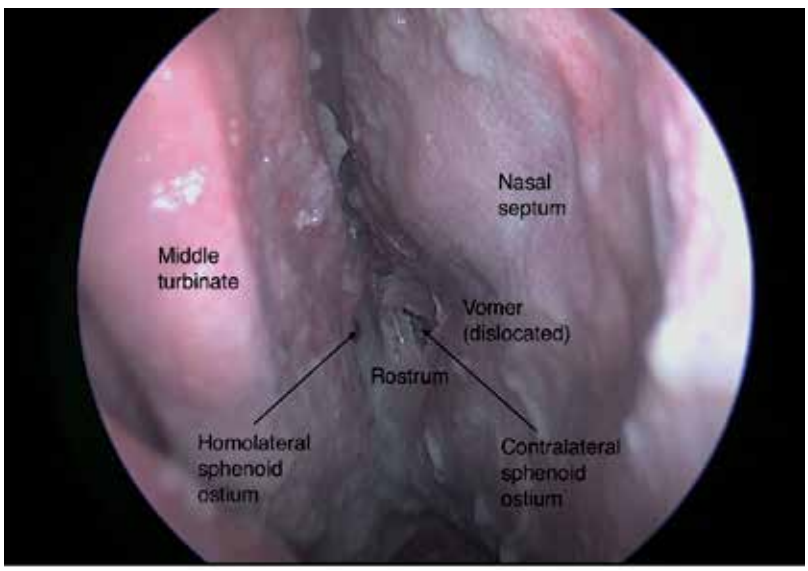

Figure 10. Cadaveric view showing sphenoid rostrum exposition after the septal mucosa is incised and the vomer is dislocated laterally. The two sphenoid ostia are here visualized, giving access to the sphenoid sinus.

The mucosa is incised with an endoscopic knife over the vomer (Figure 10) and retracted laterally until the vidian nerve, which represents the lateral limit for exposure and resection. The vidian nerve conducts in fact to the junction between the horizontal portion of the petrous ICA and the vertical paraclival segment of the ICA at the foramen lacerum.

After vomer subluxation and bilateral wide sphenoidotomies (Figure 11), the following steps of the surgery depend on the location and the extent of surgery (Figure 12). The osseous

structure of the clivus is exposed and resected through a diamond burr drill (Figure 13) and secondarily a 1 and 2 mm Kerrison bone punch, according to a cranio-caudal direction from the inferior wall of the sphenoid ostium down to the foramen magnum (Figure 14). The paraclival ICA represents the lateral limit for exposure at this level. If necessary the ICA can be carefully dissected and mobilized in the medio-lateral plane to provide adequate access to the tumor in the paramedian zone.

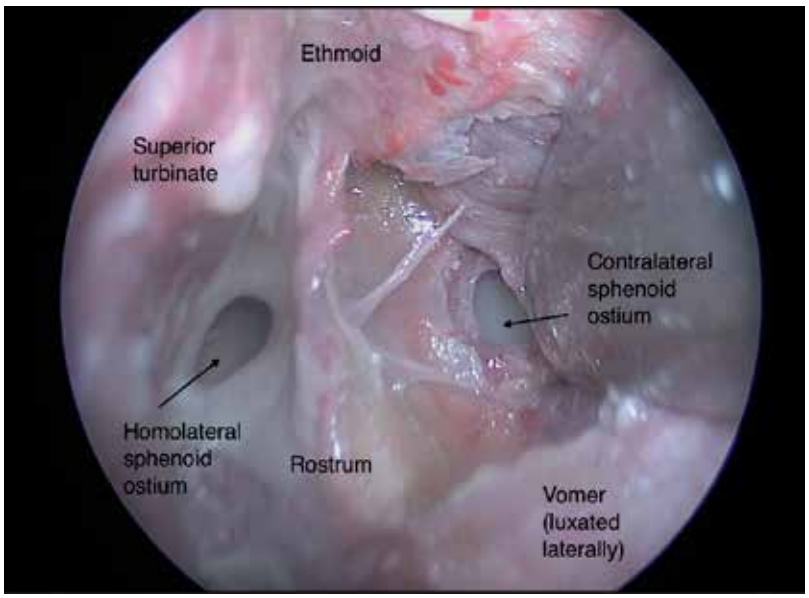

Figure 11. Bilateral exposition of the sphenoid ostia. A bilateral sphenoidotomy is then performed trhough a diamond drill and a small Kerrison bone punch to gain access to the sphenoid sinus.

The lateral extension of bone removal is defined by the pterygoid canal, which is found about 5mm lateral to the vomer-sphenoid junction. The vidian nerve may be followed proximally till the pterygoidcanal. The lateral boundaries limiting bone resection are thus represented in a craniocaudal fashion by the cavernous sinus, paraclival carotid arteries and the foramen lacerum.

The dura is thus exposed and the integrity of the basilar plexus, situated between the two layers of the dura of the upper clivus, should be respected to avoid copious bleeding. Bleeding from the basilar venous plexus is in fact often difficult to cauterize, but it may be managed with the use of hemostatic materials (Floseal Hemostatic Matrix®, Bayter Healthcare SA) and packing. The abducens nerve may be identified as traversing laterally the basilar plexus, and the paraclival ICA is also found.

For intradural lesions, a median longitudinal incision can be made initially on the outer layer of the dura. Then the internal layer is opened, with the visualization of the prepontine cistern and basilar artery (Figure 14).

http://dx.doi.org/10.5772/60553

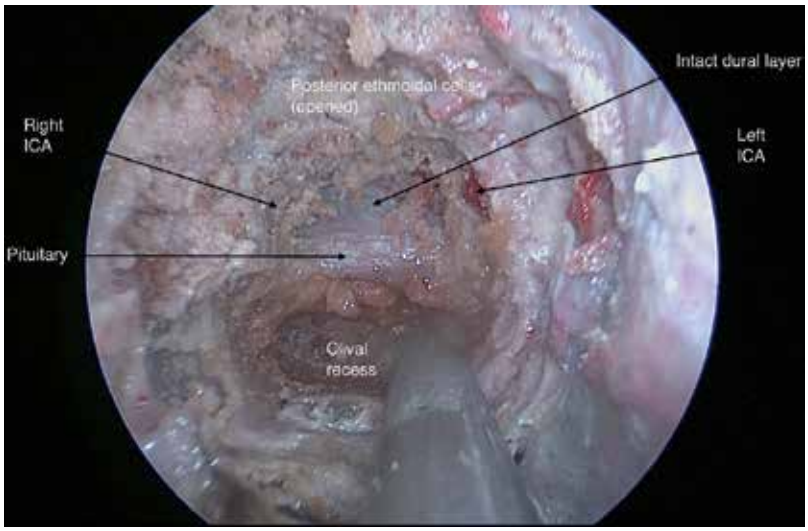

Figure 12. After a wide opening, the surgeon can choose the best sagittal corridor to reach the clival region of interest. The pituitary max be transposed to follow the supra-sellar corridor and gain access to the dorsum sellae or to the posterior clinoids or the clivus may be further drilled inferiorly. The lateral limits for the exposition are represented by the paraclival ICA. The vidian nerve should be identified and followed as it conducts directy to the foramen lacerum and may guide in defining the lateral limits of dissection.

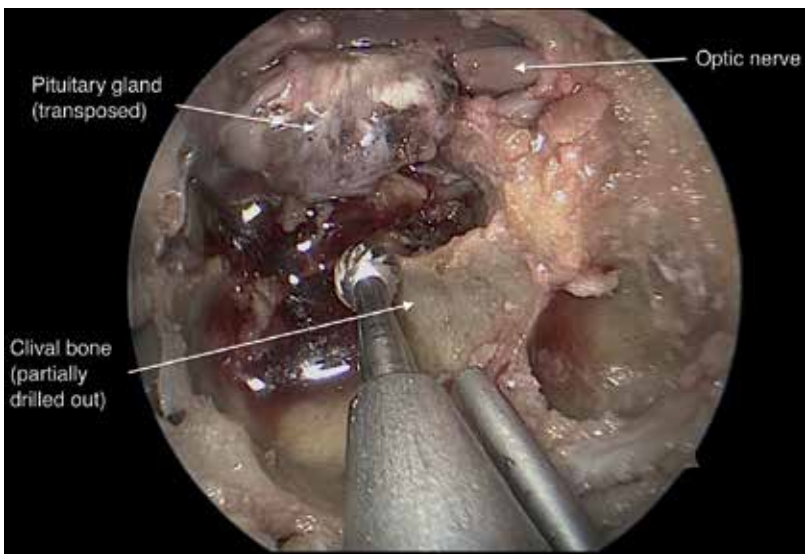

Figure 13. Drilling of the clival bone. The drilling is performed in a cranio-caudal fashion. It is important to respect dural integrity during this process.

The lesion is removed under endoscopic guidance in a piecemeal fashion with ultrasound dissectors. Intraoperative pathologic examination of tumor tissue is generally performed to decide on the extent of tumor resection on the basis of diagnosis.

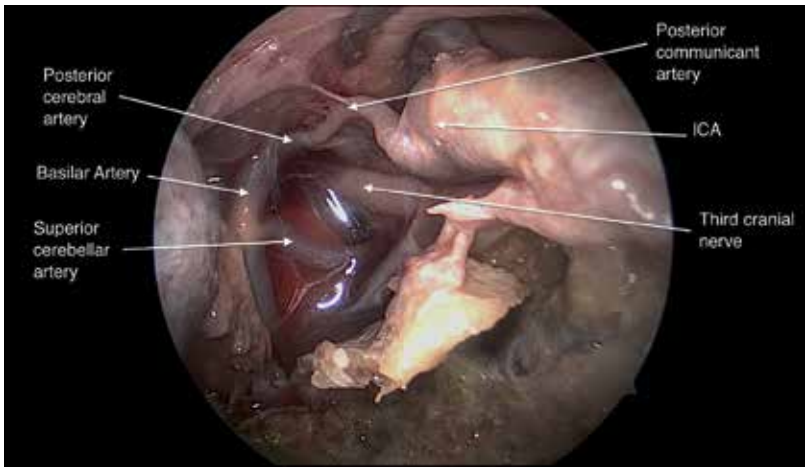

Figure 14. Exposition of the prepontine cistern in a cadaveric specimen. The two layers of the dura are opened and the posterior circulation is visualized.

The closure step is as important as the dissection and excision steps. A nasoseptal flap vascularized by the septal branches of the sphenopalatine artery may be prepared at the beginning of the procedure and displaced in the oropharynx, under the soft palate, to be protected during the surgery. It is important that the size of the pedicle of the flap stays sufficiently large to avoid necrosis of its borders. The use of the Hadad flap is now widespread, and it has allowed a significant reduction in the rate of postoperative CSF leaks after endoscopic techniques.

The reconstruction surface should be widened: flaps tend easily to shrink and we proposed the superposition of two nasoseptal flaps vascularized by branches of the posterior septal arteries in a lambdoid shape to ensure a correct closure. The middle turbinate resected at the beginning of the procedure may also be superimposed to increase the sealing in combination with biologic glue (Tisseel, Fibrin Sealant ®, Baxter AG).

3.3. Indications/management

Chordomas are slow-growing extra-axial tumors deriving from vestigial remnants of the notochord and the most common site at the sacrum and the clivus. A male predominance was described (3:1). They are considered low-grade malignancies but locally aggressive with a high recurrence rate. For this reason, gross total resection is fundamental but often difficult to achieve because of tumor extension and invasiveness and the proximity of important neurovascular structures. At clinical presentation, intracranial extension has normally occurred and complete resection is difficult in most cases (Figure 15).

When invading the basion, the most common presentation is represented by the XIIth cranial nerve palsy, while when the middle part of the clivus is interested (most common), chordomas may manifest as nasopharyngeal obstructive masses in cases of ventral extension or with VIth cranial nerve palsy in cases of dorsal extension. Chordomas arising at the upper third of the

http://dx.doi.org/10.5772/60553

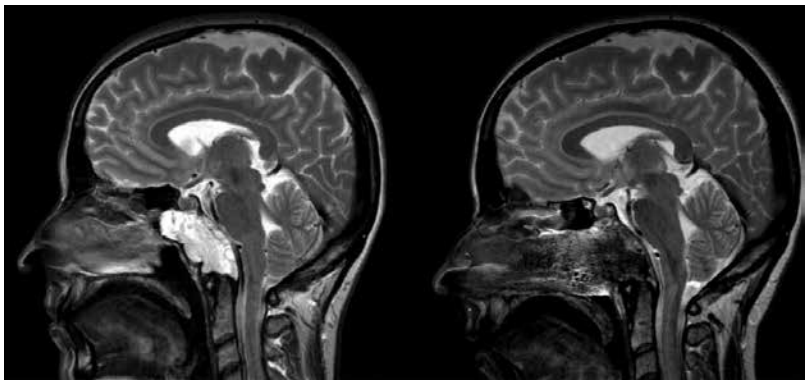

Figure 15. This young patient presented with neck pain. Preoperative sagittal T2-weighted cerebral MRI (left), showing a lesion involving the whole clivus. The sphenoidal and infrasphenoidal corridors were used to resect the lesion through EEEA. The postoperative MRI (right) shows a gross total resection of the lesion. The lesion was completely extradural. The patient was free of disease at 5-years follow-up.

clivus may present with hypopituitarism signs or bitemporal hemianopia due to chiasmal compression.

A lateral extension may also occur with consequent invasion of cavernous sinus in the upper part of the clivus or it may manifest with otologic symptoms like deafness, tinnitus and vertigo or facial paralysis because of involvement of the petrous bone.

Chondrosarcomas are malignant tumors derived from cartilaginous tissue arising from bone or soft tissues. They are less aggressive than other sarcomas but the natural history is characterized by multiple local recurrences after surgical excision. Distant metastases are rare. Both sexes are equally affected. About 75% of all cranial chondrosarcoma arise at the skull base, in particular in the middle cranial fossa. Imaging shows mottled calcifications within a soft tissue mass. Clinical manifestations are similar to those described for chordomas. Expansive lesions involving primarily the petrous apex may expand anteriorly and involve the clivus.

Meningiomas in particular may arise in close proximity to the porus acusticus or from a separate origin on the face of the petrous bone, and they may slowly extend to the clival region. They are five times more frequent in women, and the main clinical presentation is with vestibulocochlear symptoms. Secondarily, peripheral facial weakness or facial numbness are found accompanied by indirect signs of clival involvement in more advanced cases.

A complete local resection should be attempted along with resection or cauterization of dural attachment to minimize the risk of local recurrence.

The goal of every oncologic surgery should be gross total resection. However, to avoid complications and preserve neurovascular structures is the first compromise to accept when working in the clival region, and this is the first principle to guide the extent of resection.

Lesions showing wide intracavernous sinus extension, vascular encasement (ICA or vertebral artery) or brainstem involvement should be preoperatively planned as subtotal resection.

Furthermore, the extended endoscopic approach may be used as a valid alternative for debulking surgery or in palliative cases to limit the symptomatology of the patient or to allow a following complementary treatment, as radiotherapy or proton beam radiotherapy.

Traditionally clival lesions were treated through different trans-cranial approaches with a consequent important brain retraction, and a high risk of injury for the vessels and nerves crossed during the procedure [14-22].

The increased confidence in endoscopic techniques allowed a widespread application of the extended endoscopic approach to treat clival lesions. The first cadaveric study conducted in 2002 showed the feasibility of the procedure [23] and since then endoscopy has not ceased to find other applications. The main advantage is related to the avoidance of brain retraction and nerves crossing. Technological advancements allowed the development of a specialized instrumentation to work properly in the endonasal route, and many centers are pushing the application of endoscopic techniques far beyond the midline. Thanks to angled instruments, a dynamic 360° view may be obtained [24].

The results of the extended endoscopic approach for clival chordomas have been widely reported [7, 25-29]. In terms of gross total removal, it was equivalent or superior to classical open approaches [30, 31]. The extent of resection is the most important prognostic factors for survival in these cases, with a survival at 5 years of follow up dropping from 90% for GTR to 52% for partial resection [22]. The principal determinants for the surgical resection are the tumor volume and the lateral extension. The literature analysis shows how endoscopy represents an excellent approach for median lesions, with good results, especially for extradural lesions.

Following the increased experience with endoscopic techniques for extradural clival tumors, some centers started to use the trans-clival approach for the management of intradural tumors with good operative results [11, 13, 25, 31-33].

For lateral lesions or intradural lesions, however, the endoscopic approach is more complex, and it should be combined with traditional open approaches. After an excision as radical as possible, a complementary treatment through fractionated radiotherapy, stereotactic radiosurgery or proton beam radiotherapy represents the best management policy [34].

The tumor may thus be divided ideally into different compartments, which may be approached through a different surgical technique, endoscopic or transcranial, or treated with external irradiation. This conception allows minimizing the neurological morbidity and the complication rate because each technique is used safely. Furthermore, it is possible to realize a maximal resection with minimal access.

3.4. Complications

Both the extent of resection and the rate of complications are related to the experience of the first operator. The reconstructive step is as crucial as the excisional step, and it may be even more complicated in cases of large skull base defects. The first descriptive studies about the endoscopic skull base surgery reported an incidence of cerebrospinal fluid (CSF) leaks as high as 33.3% [27]. This complication may represent a medical emergency when not perceived in time because of the risk of infectious meningitis. CSF leak may be treated either with a surgical

http://dx.doi.org/10.5772/60553

revision or conservatively with a lumbar drain. The main determinant factor is the surgeon's judgment about any intraoperative source of leakage. The CSF leak rate was severely reduced during the last years after the introduction of the vascularized nasospetal flap as described by Hadad [35], the gasket type seal and the multi-layered closure technique. The lumbar drain, which once was systematically used in the early postoperative period, may thus be avoided in most cases with a precocious mobilization of patients.

Infectious complications may be treated either with medical therapy or with surgical revision.

Vascular lesions may also occur, with early or delayed hemorrhagic complications (intracranial hematoma occurred in about 6% of cases according to Carrabba et al [36]). Though a careful dissection is realized, damage to the ICA may occur, often with catastrophic results. A preoperative occlusion test may help evaluate the consequences of an eventual ICA sacrifice. The consequences of an intraoperative ICA sacrifice may vary from the death of the patients to permanent neurological deficit to a simple Horner syndrome.

Cranial nerve palsies are significantly less frequent with the endoscopic approach when compared to the open approaches and transient in the majority of cases [36]. The majority of patients report an improvement in preoperative cranial nerve palsy due to surgical decompression. After surgery, patients mostly complain about transient minor symptoms as headache, blurred vision and nasal obstruction.

Patients having a postoperative syndrome of inappropriate antidiuretic hormone hypersecretion are also reported, as well as manifestations of hypopituitarism as a consequence of pituitary manipulation.

3.5. Limitations

Classical open approaches continue to be the gold standard for lesions extending lateral to the internal carotid artery, the vertebral arteries or lateral to the optic nerve, into the mastoid or inferior to the dens.

The excision of tumors extending into the cavernous sinus is actually possible with the endoscopic technique, but the postoperative cranial nerve palsy remains significant. A subtotal resection is performed in the majority of cases and the residual tumor may be treated with adjuvant stereotactic radiosurgery.

Furthermore, for intradural tumors a combined approach (extended endoscopic endonasal approach with transcranial microsurgery) is preferred.

4. Conclusion

The expanded endoscopic approach provides a good exposure to efficiently treat lesions of the clival region. This minimally invasive technique allows obtaining satisfying results in terms of oncological resection without skin incision and neurovascular retraction in a cohort of well-selected patients.

Author details

G. Cossu[1*], R.T. Daniel[1], M. George[2], F. Parker[3], N. Aghakhani[3], M. Levivier[1] and M. Messerer[1,3]

*Address all correspondence to: giulia.cossu@chuv.ch

1 Department of Neuroscience, Neurosurgical Unit, University Hospital of Lausanne, University of Lausanne, Faculty of Medicine and Biology, Lausanne, Switzerland

2 Department of E.N.T., University Hospital of Lausanne, University of Lausanne, Faculty of Medicine and Biology, Lausanne, Switzerland

3 Department of Neurosurgery, Kremlin Bicêtre Hospital, University of Paris Sud, Faculty of Medicine, Paris, France

The authors have no personal, financial or institutional interest.

References

[1] Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies. 1990;247(2):63-76.

[2] Messerklinger W. [Role of the lateral nasal wall in the pathogenesis, diagnosis and therapy of recurrent and chronic rhinosinusitis]. Laryngologie, Rhinologie, Otologie. 1987;66(6):293-9.

[3] Cappabianca P, Cavallo LM, De Divitiis E. Endoscopic endonasal transsphenoidal surgery. Neurosurgery. 2004;55(4):933-40; discussion 40-1.

[4] Carrau RL, Jho HD, Ko Y. Transnasal-transsphenoidal endoscopic surgery of the pituitary gland. The Laryngoscope. 1996;106(7):914-8.

[5] Kassam AB, Gardner P, Snyderman C, Mintz A, Carrau R. Expanded endonasal approach: fully endoscopic, completely transnasal approach to the middle third of the clivus, petrous bone, middle cranial fossa, and infratemporal fossa. Neurosurgical Focus. 2005;19(1):E6.

[6] Liu JK, Decker D, Schaefer SD, Moscatello AL, Orlandi RR, Weiss MH, et al. Zones of approach for craniofacial resection: minimizing facial incisions for resection of anterior cranial base and paranasal sinus tumors. Neurosurgery. 2003;53(5):1126-35; discussion 35-7.

[7] Kassam AB, Prevedello DM, Thomas A, Gardner P, Mintz A, Snyderman C, et al. Endoscopic endonasal pituitary transposition for a transdorsum sellae approach to the interpeduncular cistern. Neurosurgery. 2008;62(3 Suppl 1):57-72; discussion 4.

[8] Kassam AB, Vescan AD, Carrau RL, Prevedello DM, Gardner P, Mintz AH, et al. Expanded endonasal approach: vidian canal as a landmark to the petrous internal carotid artery. Journal of Neurosurgery. 2008;108(1):177-83.

[9] Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part I. Crista galli to the sella turcica. Neurosurgical Focus. 2005;19(1):E3.

[10] Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part II. Posterior clinoids to the foramen magnum. Neurosurgical Focus. 2005;19(1):E4.

[11] Cappabianca P, Cavallo LM, Esposito F, De Divitiis O, Messina A, De Divitiis E. Extended endoscopic endonasal approach to the midline skull base: the evolving role of transsphenoidal surgery. Advances and Technical Standards in Neurosurgery. 2008;33:151-99.

[12] De Notaris M, Cavallo LM, Prats-Galino A, Esposito I, Benet A, Poblete J, et al. Endoscopic endonasal transclival approach and retrosigmoid approach to the clival and petroclival regions. Neurosurgery. 2009;65(6 Suppl):42-50; discussion 2.

[13] Schwartz TH, Fraser JF, Brown S, Tabaee A, Kacker A, Anand VK. Endoscopic cranial base surgery: classification of operative approaches. Neurosurgery. 2008;62(5): 991-1002; discussion 5.

[14] Al-Mefty O, Ayoubi S, Smith RR. The petrosal approach: indications, technique, and results. Acta Neurochirurgica Supplementum. 1991;53:166-70.

[15] Asaoka K, Terasaka S. Combined petrosal approach for resection of petroclival meningioma. Neurosurgical Focus. 2014;36(1 Suppl):1.

[16] Goel A, Desai K, Muzumdar D. Surgery on anterior foramen magnum meningiomas using a conventional posterior suboccipital approach: a report on an experience with 17 cases. Neurosurgery. 2001;49(1):102-6; discussion 6-7.

[17] Hakuba A, Liu S, Nishimura S. The orbitozygomatic infratemporal approach: a new surgical technique. Surgical Neurology. 1986;26(3):271-6.

[18] Javed T, Sekhar LN. Surgical management of clival meningiomas. Acta Neurochirurgica Supplementum. 1991;53:171-82.

[19] MacDonald JD, Antonelli P, Day AL. The anterior subtemporal, medial transpetrosal approach to the upper basilar artery and ponto-mesencephalic junction. Neurosurgery. 1998;43(1):84-9.

[20] Samii M, Knosp E. Approaches to the Clivus: Approaches to No Man's Land. Berlin: Springer-Verlag Berlin and Heidelberg GmbH & Co. K; 23 December 2011. p. 184.

[21] Seifert V, Raabe A, Zimmermann M. Conservative (labyrinth-preserving) transpetrosal approach to the clivus and petroclival region--indications, complications, results and lessons learned. Acta Neurochirurgica. 2003;145(8):631-42; discussion 642.

[22] Sen C, Triana AI, Berglind N, Godbold J, Shrivastava RK. Clival chordomas: clinical management, results, and complications in 71 patients. Journal of Neurosurgery. 2010;113(5):1059-71.

[23] Alfieri A, Jho HD, Tschabitscher M. Endoscopic endonasal approach to the ventral cranio-cervical junction: anatomical study. Acta Neurochirurgica. 2002;144(3):219-25; discussion 25.

[24] Cappabianca P, Alfieri A, De Divitiis E. Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). Minimally Invasive Neurosurgery : MIN. 1998;41(2):66-73.

[25] Stippler M, Gardner PA, Snyderman CH, Carrau RL, Prevedello DM, Kassam AB. Endoscopic endonasal approach for clival chordomas. Neurosurgery. 2009;64(2): 268-77; discussion 77-8.

[26] Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. Neurosurgery. 2006;59(1 Suppl 1):ONS50-7; discussion ONS7.

[27] Dehdashti AR, Karabatsou K, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for treatment of clival chordomas: early results in 12 patients. Neurosurgery. 2008;63(2):299-307; discussion 9.

[28] Hong Jiang W, Ping Zhao S, Hai Xie Z, Zhang H, Zhang J, Yun Xiao J. Endoscopic resection of chordomas in different clival regions. Acta Oto-Laryngologica. 2009;129(1):71-83.

[29] Solares CA, Fakhri S, Batra PS, Lee J, Lanza DC. Transnasal endoscopic resection of lesions of the clivus: a preliminary report. The Laryngoscope. 2005;115(11):1917-22.

[30] Al-Mefty O, Borba LA. Skull base chordomas: a management challenge. Journal of Neurosurgery. 1997;86(2):182-9.

[31] Fraser JF, Nyquist GG, Moore N, Anand VK, Schwartz TH. Endoscopic endonasal minimal access approach to the clivus: case series and technical nuances. Neurosurgery. 2010;67(3 Suppl Operative):ons150-8; discussion ons8.

[32] Cavallo LM, Messina A, Gardner P, Esposito F, Kassam AB, Cappabianca P, et al. Extended endoscopic endonasal approach to the pterygopalatine fossa: anatomical study and clinical considerations. Neurosurgical Focus. 2005;19(1):E5.

http://dx.doi.org/10.5772/60553

[33] Cavallo LM, Messina A, Cappabianca P, Esposito F, De Divitiis E, Gardner P, et al. Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. Neurosurgical Focus. 2005;19(1):E2.

[34] Daniel RT, Tuleasca C, Messerer M, Negretti L, George M, Pasche P, et al. Optimally invasive skull base surgery for large benign tumors. In: Berouma M, editor. Minimally Invasive Skull Base Surgery: Nova Science Publishers, Inc.; 2013.

[35] Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. The Laryngoscope. 2006;116(10):1882-6.

[36] Carrabba G, Dehdashti AR, Gentili F. Surgery for clival lesions: open resection versus the expanded endoscopic endonasal approach. Neurosurgical Focus. 2008;25(6):E7.

Miscellaneous

Chapter 16

Office Hysteroscopy

Pados George and Makedos Anastasios

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60658

Abstract

Hysteroscopy is the most accurate technique in order to visualise the endometrial cavity and diagnose relevant pathologies. Despite the further evolvement of ultrasonography, hysteroscopy provides not only diagnosis but also treatment, when needed. Based on fine hysteroscopes produced recently, hysteroscopy can be easily performed in an office-based environment, not only for diagnostic but also for treatment of minor pathologies. The more attractive office environment compared with the conventional operating theater, the no-need for general anaesthesia and the reduced cost compared to the classic hysteroscopy are the main advantages that characterize office hysteroscopy and that made it more popular during the last years.

Keywords: Office, hysteroscopy, diagnostic, operative, minimal invasive surgery

1. Introduction

The evolution of the medical technology during the last decades has introduced hysteroscopy in the everyday clinical practice, for the visualization of the endometrial cavity for diagnostic and also operative purposes. This has led to the precise management of gynecological problems in the field of infertility, recurrent miscarriages, postmenopausal bleeding, uterine cancer, and menstrual disorders. Although transvaginal ultrasound scanning in 2D and 3D mode are considered useful tools for first line screening, the gap between precise diagnosis before treatment was covered by the introduction of a fine hysteroscope, which provides more accurate information. Nevertheless in most cases operative hysteroscopy substituted the blind technique of dilation and curettage, solely used over the past years.

Office hysteroscopy is a very useful technique for diagnosis and treatment of uterine pathology in an office-based environment (Figure 1). It is directly related to the technological explosion, which during the last years has further evolved and given us the opportunity to perform hysteroscopy without providing general anesthesia or sedation to the patients, due to the narrow width of the latest generation hysteroscopes. This means that after adequate and thorough experience and toward the reduction of the cost and satisfaction of the patients, hysteroscopy in an outpatient environment, called office hysteroscopy, has started to attract the majority of gynecologists.

The aim of this chapter is to familiarize the clinicians in the field of gynecology with the instrumentation and setup, the technique itself, indications, and contraindications for performing office hysteroscopy and finally the advantages for the patient and the clinician who perform this endoscopic approach.

Figure 1. Typical setup for office hysteroscopy in a private office-based practice

http://dx.doi.org/10.5772/60658

2. Instruments

2.1. Hysteroscopes

There are two different types of hysteroscopes available. The rigid hysteroscopes are composed of two parts, the scope and the outer sheath with a total diameter of 2.9–4 mm (Figure 2, Figure 3). The outer sheath comes with suction and irrigation valves, which allows the inflow and outflow of the distension medium of the uterine cavity and can be mounted on an irrigation-suction device. Further, there is an operating channel from which specifically designed instruments can go through for operative purposes or retrieval of endometrial tissue for biopsy. The advantages are that they are exactly the same as the non-office hysteroscopes, so for a clinician who is experienced in hysteroscopy there is no learning curve, and they can be used without inserting a vaginal speculum (no-touch technique or vaginoscopic approach). Furthermore, they can be used with suction device, while a great variety of instruments are specifically designed for these and the scopes are available in 12, 25, or 30 degrees angular vision. In the disadvantages we need to mention that they come in many parts and also the optics are very thin, from 2 mm in diameter, which makes them very fragile during cleaning and disinfection, while there is an existing risk of uterine perforation due to the rigidity. Finally, they have greater width compared with the flexible hysteroscopes.

Figure 2. Operative hysteroscope for office hysteroscopy

The flexible hysteroscopes (Figure 4) are compact without any additional part, even the light source cable is permanently fixed on these. They do not come with an outer sheath, which means that they lack suction mechanism but there is a working channel, through which flexible instruments can be inserted and used for biopsy and minor surgical procedures. The visual angle is up to 120 degrees due to the flexibility, so there is no external manipulation of the hysteroscope, which can minimize the discomfort of the patient. Cleaning, disinfection, and storage are simpler than the rigid ones. The possible perforation of the uterus is quite non-existing, but on the contrary during insertion the scope might be obstructed by even loose adhesions or endometrial structures such as large polyps or fibroids. In practice, and from our experience, it means that it is preferable to dilate the cervical canal before insertion with a thin dilator. The vaginoscopic approach is more difficult to be performed with a flexible hysteroscope compared to the rigid ones and therefore in all cases the use of a vaginal speculum is needed but on the other hand the use of a tenaculum for straightening the cervical canal is

almost never needed, as long as due to the flexibility the scope can easily go through all types of uterus (anteverted, retroverted, etc.). Finally, there is clear evidence that in procedures where flexible hysteroscopes are used patients experience less pain and discomfort [1].

Figure 3. Distal part of an office operative hysteroscope

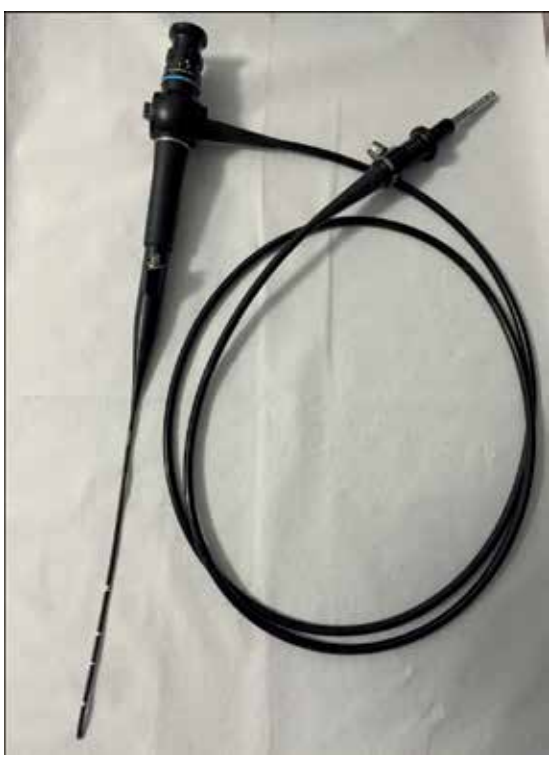

Figure 4. Flexible hysteroscope of 3.1 mm total diameter

http://dx.doi.org/10.5772/60658

3. The setup

The basic setup in order to perform an office hysteroscopy consists of a camera, a camera control unit connected to a -DVD recording device, a light source, and a monitor, connected exactly the same way as in the operating theater, all of them placed on an equipment cart, or there are also compact devices where all the above mentioned come as a single appliance. An irrigation-suction unit for the distension medium can be used, but for diagnostic purposes a handcuff with a manual air pump can be used for irrigation, around the bottle of the distension medium, as long as for experienced clinicians the whole procedure will last less than 5 minutes and the amount of the distension medium to be used will be less than 200 ml. Additional equipment ready for use can be a dental syringe fitted with a sealed cartridge containing anesthetic solution for cervical local anesthesia and a plastic cervical dilator, a vaginal speculum, sterile gauges, and a forceps in order to control spotting bleeding from the cervix, after injection of local anesthetic, all placed on a secondary equipment cart. The patient is placed on a gynecological chair, in lithotomy position that will allow the clinician to perform manipulations with the hysteroscope without restrictions. It is advised that a flat examination bed is also present in the same room, in case of vasovagal reaction after the end of the procedure. A typical setup is shown in Figure 1. Finally it is advised that a chaperon is present during the procedure, but in terms of assistance the setup described is ideal for a single person to perform.

4. Analgesia/anesthesia

There is no clear evidence that local anesthesia should be used prior to office hysteroscopy, while results from several studies cannot reach a definite conclusion. Nevertheless in cases of non-vaginoscopic procedures from our experience, we strongly recommend the proposal of cervical local anesthetic, which can possibly lead to less pain experienced by the patients, especially if cervical dilatation is needed, but also gives a feeling of confidence to the patients before getting through the procedure. Moreover, in cases where the use of tenaculum is needed, local cervical anesthesia should be applied [2]. It should be mentioned that use of intracervical or paracervical local anesthesia for preventing vasovagal reactions is not an indication.

Conscious sedation should not be used as it does not contribute to pain control more than local anesthesia and also dangerous complications that may occur cannot be controlled in an office-cased environment [3].

As far as analgesia is concerned, it is recommended that NSAIDS (non-steroidal anti-inflammatory drugs) should be used an hour prior to the procedure for pain relief but the use of opioids should be avoided as they may have adverse effects like nausea, vomiting, and drowsiness [2].

In general the choice for analgesia prior or during the procedure should be decided by the clinician according to the patient's history, possible vasovagal reaction in the past, the

condition of the uterine cervix (nulliparous or multiparous), and the reluctancy of the patient regarding the possible pain that she may experience during the procedure. All the choices should be offered to the patients during the consent procedure.

5. Distention medium

Office hysteroscopy can be performed with the use of normal saline solution or CO2. It is advisable that the choice of the medium is at the discretion of the clinician. Nevertheless, there seem to be advantages from the use of normal saline as long as it can provide better visibility and clearing out of blood clots and debris, less possible vasovagal reactions (sickness, bradycardia, and hypotension) from the patients, and also the setup is more simple and more practical compared to CO2. Furthermore, the use of normal saline does not offer reduction of pain but can lead to quicker procedures [4,5], but the latter is clearly affected also by the clinician's experience with the medium and the procedure itself.

6. Types of office hysteroscopy

6.1. Diagnostic office hysteroscopy

Office hysteroscopy is the most accurate diagnostic tool for endometrial pathologies and a second line tool after primary diagnosis deriving from 2D or 3D transvaginal ultrasound scan. Compared to the hysteroscopy performed in the operating theater under general anesthesia or sedation, there are clear benefits for the patients, such as the avoidance of taking general anesthesia, especially for patients who are at high-risk for anesthetic complications. The reduced time of the whole procedure and also the location, especially when performed in an out-of hospital environment, are crucial for the patients in order to decide. Also, the reduced cost of around 40–60%, as long as hospital and anesthetic costs are excluded, attracts more patients and also more clinicians to propose, especially in current years of financial recession. Finally the provision of this diagnostic tool in an office-based environment gives an added value to the private practice and its services, but also assists the clinicians to provide more than one choice to their patients.

Indications for diagnostic office hysteroscopy can be categorized for premenopausal and postmenopausal women.

6.1.1. Premenopausal women

Abnormal uterine bleeding is an indication for office hysteroscopy, if there is clear evidence of pathology at the ultrasound scan. The authors recommend that before proposing the technique, if there are no obvious ultrasonographic findings, it is wise to exclude any other endocrine, ovarian, or cervical pathology.

http://dx.doi.org/10.5772/60658

In terms of infertility investigation, office hysteroscopy is very useful in the investigation of the endometrial cavity in women who underwent two complete cycles of in vitro fertilization (IVF) – two failed implantations, even if there is no ultrasonographic evidence. The same indication stands for women with recurrent miscarriages – more than three consecutive miscarriages. Small endometrial polyps, uterine septae, endometrial adhesions, and cervical adhesions are common findings, which can be revealed with hysteroscopy. This approach is, also, very useful for the evaluation of the quality of the endometrium during the luteal phase.

Women who take tamoxifen as a regime for breast cancer are in need of endometrial assessment by biopsy and thus hysteroscopy is not an absolute indication, but in cases where endometrial thickness is ≥ 8 mm it is highly recommended in order to exclude an endometrial polyp or ongoing endometrial cancer [6].

6.1.2. Postmenopausal women

Postmenopausal women with uterine bleeding should be investigated with office hysteroscopy regardless of the ultrasonographic findings, which apart from benign pathologies can lead to the diagnosis of uterine or cervical cancer. In cases of cancer the benefit of accurate diagnosis outweighs the risk of spreading neoplastic cells into the abdominal cavity and thus dilatation and curettage is advised not to be preferred over hysteroscopy [7]. A finding of an endometrial polyp in postmenopausal women is not a rare finding.

6.2. Operative office hysteroscopy

Operative procedures performed in an office-based environment are quite limited. There is no specific guideline regarding operative procedures but usually minor procedures such as endometrial biopsies, removal of endometrial polyps, dissection of loose intrauterine adhesions, removal of intrauterine devices with a missing thread or foreign objects and also for permanent tubal sterilization with the insertion of tubal coils (Essure®) are performed in the everyday clinical practice and are well tolerated by the patients. Operative office hysteroscopy can be an extension of diagnostic office hysteroscopy, as long as there are no special setup requirements and cervical preparation is not needed.

Contraindications for both diagnostic and operative hysteroscopy are heavy uterine bleeding or menstruation, vaginal infection, active pelvic inflammatory disease, and history of adverse reactions during a previous office hysteroscopy. As mentioned earlier, suspicion of cancer is not a contraindication for performing diagnostic hysteroscopy and biopsy.

7. Advantages and disadvantages of office hysteroscopy

7.1. For the patient

Office hysteroscopy is mainly designed for the patient's advantage. The use of hysteroscopy in an office-based environment, especially in the "one-stop" clinic, in a hospital or in a private

practice, can give fast and accurate diagnosis and treatment without waiting lists and at a substantially lower cost, as hospital and anesthetic costs are excluded. Without the use of sedation or anesthesia, patients can go back to their everyday activities just after the end of the procedure. The disadvantage of the possible discomfort during the procedure or the cramp-like lower abdominal pain after are outweighed by the benefits that the patients can have.

7.2. For the clinician

For the clinicians in the fields of gynecology, infertility, and gynecological oncology, office hysteroscopy is the ultimate tool for accurate diagnosis of endometrial pathologies. A future management plan can be easily scheduled after the end of the procedure, unless a further pathology report from biopsies is expected.

Regarding the diagnosis, from our experience, miniature hysteroscopes with a low width inflow channel for the distention medium provide low pressure distention of the uterine cavity and so in cases of soft tissue structures like polyps, adenomyomas, and fundal adhesions we get a first more realistic depiction of the uterine cavity.

Of course the setup in a private practice is not time-consuming, as long as the time needed for the setup arrangements before and after the procedure is many times more than the procedure itself and so it is suggested that a special separate room or appointment on a specific day should be used, if the same room is to be used after for other examination purposes. In general though, in a private gynecological practice, application of office hysteroscopy extends the list of the provisional services and gives the clinician an added value, though even in our days the technique is not very widespread.

8. Discussion

Office hysteroscopy is the undoubtful gold-standard tool for the investigation of the uterine cavity. It is a technology-based technique that has greatly evolved during the last decade, and there is still place for further improvements. Ideas for change come from the gynecologists, through the everyday practice, and should be addressed to the manufacturing companies in the field.

For the clinicians who want to apply hysteroscopy in an office-based environment, the training is much shorter and easier if they had previous training and experience in hysteroscopy under general anesthesia. This, on the other hand may restrict many clinicians from getting involved for the first time with diagnostic office hysteroscopy, which is a simple and low-risk technique. This reluctance may also derive from up-to-date guidelines, which are unclear in specific details as the type of hysteroscope to choose, provision of local anesthesia or not.

Practically, from the patient's point of view and against all the benefits that office hysteroscopy provides, the only fear is the experience of pain and discomfort during the procedure. On the contrary pain intensity is a subjective evidence described in relative research, thus local

anesthetic should always be discussed with the patients when consenting and provided according to the possible length of the procedure.

The use of flexible hysteroscopes result in less painful diagnostic procedures compared to the rigid one, so for a clinician who will only perform diagnostic hysteroscopy in the office seems like a better choice, though taking into consideration that the learning curve is longer, compared to the rigid hysteroscope.

Clinicians in the field of gynecology who are reluctant against the technique should get more familiar with office hysteroscopy where training is available, courses or any type of medical literature. Further research will probably clarify some details and assist the clinicians to take the right decisions for providing the best possible care according to the patients' needs. We assume that in the near future almost all diagnostic and minor operative hysteroscopic procedures will be solely performed in an office-based environment either inside a hospital or in a private practice.

9. Conclusions

It is evident that office hysteroscopy enables the clinician to perform not only diagnostic but also minor operative procedures in an office setting with less risk, low cost, and better results. The near future comprises improvements in the hysteroscopic instrumentation, new energy supplies, and new systems for controlling intrauterine pressure, which will yield further benefits for the patients and the clinicians.

Author details

Pados George and Makedos Anastasios

*Address all correspondence to: padosgyn@hol.gr

1st Dept. OB-GYN, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital, N. Efkarpia, Greece

References

[1] Unfried G, Wieser F, Albrecht A, Kaider A, Nagele F. Flexible versus rigid endoscopes for outpatient hysteroscopy: a prospective randomized clinical trial. Hum Reprod 2001;16:168–71.

[2] Best Practice in Outpatient Hysteroscopy. Green-top Guideline No. 59. RCOG/BSGE Joint Guideline.

[3] Guida M, Pellicano M, Zullo F, Acunzo G, Lavitola G, Palomba S, et al. Outpatient operative hysteroscopy with bipolar electrode: a prospective multicentre randomized study between local anaesthesia and conscious sedation. Hum Reprod 2003;18:840–3.

[4] Cooper NA, Smith P, Khan KS, Clark TJ. A systematic review of the effect of the distension medium on pain during outpatient hysteroscopy. Fertil Steril 2011;95:264–71.

[5] Shankar M, Davidson A, Taub N, Habiba M. Randomised comparison of distension media for outpatient hysteroscopy. BJOG 2004;111:57–62.

[6] Franchi M, Ghezzi F, Donadello M, Zanaboni F, Beretta P, Bolis P. Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease. Obstet Gynecol 1999;93:1004–8.

[7] Zhu HL, Liang XD, Wang JL, Cui H, Wei LH. Hysteroscopy and directed biopsy in the diagnosis of endometrial carcinoma. Chin Med J 2010;123:3524–8.

Chapter 17

Endoscopy in Renal Cancer Organ Preservation Treatments

J.G. Calleary, T. Lee, B. Burgess, R. Hejj and P. Naidu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60543

Abstract

This chapter traces the shift in treatment of localised renal cancer from major open surgery to endoscopic (ie laparoscopy) techniques. It also details the shift in treatment intent for localised Renal cancer toward Organ preservation. With advancement in technology and experience, the principles of endoscopic surgery have been adapted to treat renal malignancy with minimum complications and with maximal preservation of Renal function so much so that endoscopic techniques are seen as the "gold standard" by many. The chapter details these minimally invasive techniques of laparoscopic and Robotic partial nephrectomy and compares and contrasts both Oncological and Functional outcomes from both.

Keywords: Renal Cancer, Prostate cancer, Minimally invasive Surgery, Focal therapy, Partial Nephrectomy

1. Introduction

Urology is rapidly becoming a speciality where operative treatment of disease is primarily endoscopically administered The two last bastions of open surgical procedures in urology were reconstruction and radical surgical treatment of malignancy. In uro-oncology and in intra-abdominal reconstructive procedures such as Pelvi-Ureteric Junction (PUJ) obstruction, minimally invasive techniques are rapidly becoming the norm and indeed the debate is about which endoscopic technique results in the best outcomes [1]. From being the standard, open techniques are now limited to the worst locally advanced malignancies or revision recon-

structive procedures. This review will chart the course of endoscopy in the treatment of localised RCC and especially in the era where organ preservation techniques have become paramount.

2. From open to Laparoscopic Radical Nephrectomy (LRN)

Perhaps the area which best illustrates this shift in emphasis in uro-oncology from open procedures to endoscopy is the treatment of localised Renal Cell Cancer. Robson et al. demonstrated improved survival established using open Radical Nephrectomy (all tissue within Gerotas fascia and ipsilateral adrenal and nodal tissue), and the technique became the gold standard treatment for localised renal cell cancer (T1–T2, see table 1 [2]. For about two decades, this remained the case, but there were concerns regarding complication rates and increased patient dissatisfaction, especially with flank incisions. An illustrative example of the latter is Chatterjee's work from 2004, which showed a 50% dissatisfaction rating vis-à-vis flank bulging and approximately 25% with ongoing wound pain [3].

In the early 1990's, the first laparoscopic procedures on the kidney were performed [4]. As experience with the technique grew and with favourable reports, it became the preferred choice. By mid to late 2000s, laparoscopic nephrectomy was the new gold standard after numerous studies demonstrated equivalent oncological outcomes in addition to enhanced patient experience. An example is the case-controlled study of Dunn et al. wherein equivalent short-term oncological outcomes were demonstrated in a comparative study of open and laparoscopic nephrectomy.

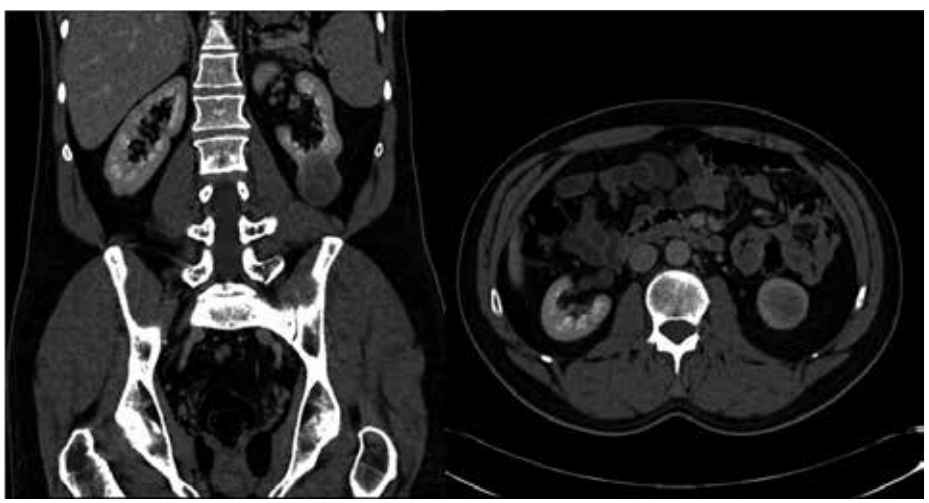

Figure 1. Two slices from a CT series to show a lesion treatable by partial nephrectomy (PN). This is a predominantly exophytic and polar lesion but it does cross the lower sinus line and probably involves the collecting system, thus making it a more complicated lesion than at first appearance.

http://dx.doi.org/10.5772/60543

However, laparoscopic nephrectomy was associated with more than a 50% reduction in blood loss, analgesic requirement, hospital stay and time to return to normal activities [5]. This low complication rate (eg bleeding rate of 2.8% and transfusion rate of 0.7%) was confirmed by a 2006 meta-analysis. The conversion rate was 2.5% and colonic injury was 1.5% [6]. This difference persists to the present day with Xu et al. showing a significant reduction in Claivan grade 2 complications, a 36% reduction in all complications and a 17% reduction in length of hospital stay [7]. Luo`s study published in 2010 confirmed the long-term oncological equivalence [8].

	Primary lesion
TX	Not assessable
T1a	0–4 cm diameter, limited to kidney
T1b	4–7 cm, limited to kidney
T2a	7–10 cm, limited to kidney
T2b	> 10 cm, limited to kidney.
T3a	Renal vein or segmental branch invasion Peri-renal / Renal sinus invasion confined to gerotas fascia
T3b	Invasion of IVC below diaphragm
T3c	Invasion of IVC above diaphragm Direct IVC wall invasion
T4	Invasion beyond Gerotas fascia Direct invasion of Ipsilateral Adrenal
	Regional Nodes
NX	Not assessed
N0	None
N1	Single node involved
N2	> single node involved
	Metastatic disease
M0	None
M1	Present

Table 1. TNM staging of Renal Cell Cancer (2009) – EAU Guidelines [9]

3. Organ preservation

As laparoscopic nephrectomy was becoming more widely practiced, two separate trends conspired against this endoscopic technique. The first was a stage migration of renal masses

(i.e. presumed cancers) downward, which coincided with an increased incidence secondary to incidentally imaging (US and CT) detected lesions [10-11]. Allied to this was the increased identification of benign pathology in nephrectomy specimens performed for these small masses, which approached 20% in some series.

The second was an increasing realisation that the adverse effect of radical nephrectomy on renal function may result in reduced survival because of an association with cardiac mortality. Go et al. published a sentinel paper in the NEJM, which followed 120,295 adults over five years. Increased mortality, increased risk of vascular and cardiac disease and hospitalisations were significantly more common in those with chronic renal impairment (e GFR < 60 ml/min/ 1.73 m2) [12]. It was well documented that radical nephrectomy was associated with the development of renal failure. In 2006, Huang et al. demonstrated a reduction in the probability of developing new renal failure from 65% to 20% by the use of Nephron sparing Surgery (NSS) [13].

Studies like the above lead to an increasing search for alternatives to RN for T1a (< 4 cm) and T1b RCC (< 7 cm). NSS was the most extensively researched and in time has become a gold standard, especially for T1a lesions. It also led to the introduction of ablative technologies such as cryotherapy, HIFU (High-Intensity Focused Ultrasound) and RFA (Radio Frequency Ablation).

Partial Nephrectomy (table 2-3)

The aim of partial nephrectomy is the complete removal of the detected lesion with a margin of normal tissue of as little as 1 mm and as little damage to the remaining renal tissue as possible. Confirmation of a negative margin often requires frozen section analysis of the specimen. The initial indications for partial nephrectomy were tumours in a solitary kidney, multiple/ bilateral tumors or patients with poor renal function (table 3).

T stage	Recommendation
T 1a	Partial Nephrectomy (PN) is the preferred option
T 1b	Radical Nephrectomy (RN) or PN
T2	Radical Nephrectomy Partial Nephrectomy is associated with greater chance of local failure

Table 2. Accepted indications for PN

Absolute	**Lesions in a single Kidney** **Bilateral synchronous lesions** **T1a lesions with low PADUA scores (see page 6)**
Relative	T1b /T2 lesions with a normal contra-lateral Kidney but significant potential of future renal failure due to comorbidities Hereditary RCC
Elective	T1/ T2 lesion; other kidney normal, no “reno-toxic” comorbidity

Table 3. EAU guidelines for surgical treatment of localised Renal Cell Cancer (RCC) [9]

http://dx.doi.org/10.5772/60543

Traditionally, this involved dissection of the renal pedicle and subsequent clamping of the renal artery (± renal vein). This results in reduced blood loss and a reduced tissue tension, which makes dissection easier and improves visualisation. The perirenal fat is removed from the relevant area apart from directly over the lesion. The lesion is excised and the collecting system repaired. The kidney is then repaired and when done so satisfactorily, the clamp is removed.

Unfortunately, clamping is associated with ischaemia, which led to techniques to reduce the effects of ischaemia, and the concept of hypothermia following preconditioning prior to clamping with mannitol was introduced. The purported effect of mannitol is as promoter of renal vasodilation, thus promoting blood flow. It also prevents cast formation and decreases post-ischaemic swelling [14]. Hypothermia aims to get the renal core temperature to 15–20^{0}C and is achieved by cooling with ice slush for 10–15 minutes post clamping. This slows metabolism down to minimise the effects of ischaemia.

Initially this was thought to be possible only using open techniques, which meant a reduction in laparoscopic renal cancer procedures, although this tended to be mainly driven by academic centres. With time, the use of PN spread and Kim et al. using a US nationwide dataset showed the percentage of small renal masses treated by RN fell from 85% to 75% in the period from 2002 until 2008 [15].

The initial studies confirmed that OPN produces equivalent oncological outcomes compared to RN. Lau et al. showed equal cancer-specific survivals for both groups and metastatic disease in less than 5% of both RN and OPN groups in the case-controlled study of 164 patients in each group [16]. Similarly, Tan et al. showed excellent long-term cancer-specific survival again comparable to RN. Using the SEER database, they compared outcomes for 1925 PN against 5213 RN and showed similar RCC mortality from both PN (1.9%) and RN (4.3%) [17].

A significant proportion of the early debate in OPN focused on the question of the determinants of local recurrence and the potential effect on survival. One such risk is a positive surgical margin and Yossepowitch estimated that to happen in 2–8% of OPN [18]. Thankfully, this does not appear to have a survival impact, judging by the review of Van Popell and Joniou [19]. They have suggested that a 1 mm clear margin is enough to prevent local recurrence. An alternative technique practiced by some is lesional enucleation. This would be expected to be associated with greater local failure, but from the study of Minnervi et al., this would appear not to be the case [20]. Similarly, good oncological outcomes are achieved where PN is performed for lesions up to 7 cm [21].

Much of the early work on partial nephrectomy was done by the Cleveland Clinic group, especially by Novick and Gill. Some of their initial work confirmed the hypothesis that LRN was associated with significantly worse renal function (as measured by serum creatinine) at follow up albeit with reduced peri-operative complications in terms of bleeding, analgesia requirement and hospital stay. However, the two groups were not well matched as the LN group were significantly older, of greater comorbidity (as judged by ASA score) and had larger masses [22]. By the time Lesage`s review paper came out in 2007, the gap had narrowed and the complication rates were not significantly different, although there was a trend towards

greater complications in the OPN groups. Importantly, the significantly increased risk of renal failure with RN compared to PN was confirmed [23]. Up to 22% of LRN patients had insufficiency at 10 years compared to at most 11.6% of the OPN group [16].

There are three factors, which contribute to renal function loss post any renal surgical intervention. These are pre-operative renal function (including comorbidity affecting renal function), the volume of excised/ damaged renal tissue and any intraoperative surgical ischaemia (be this warm or cold ischaemia). Of these, it is the ischaemia time which is the only variable open to surgical control. Warm ischaemia time (WIT) is defined as the length of time the blood supply is cut off or reduced at body temperature. Essentially, this equates to clamping time. Cold ischaemia time (CIT) is the time between when a tissue is cooled, has its blood supply reduced or cut off and is then re-warmed to body temperature [24].

It was because of the absolute centrality of clamping (and therefore a resultant ischaemic insult) to PN that the pendulum swung back to open surgery. This was the case even in centres that were pioneers in the field of PN and laparoscopic urology. IS Gill in an editorial in December 2012 stated of his time working with Dr. Novick at the Cleveland Clinic that *"never did we even discuss the possibility of doing major PN surgery without clamping the main renal artery" [25].*

As experience with PN grew and it became clear that PN was associated with superior functional and equivalent oncological outcomes, research shifted to focus on what if any was the limit of WIT and on methods to reduce ischaemic time. It is worth noting the primary tasks, which have to be completed during this time. These are removal of the lesion with a negative margin. The second is the repair of any collecting system injury, which may be checked by intravenous administration of indigo carmine and thirdly, the closure of the kidney using continuous sutures and adjunct measures. As can be imagined, the more complicated the lesion (larger, centrally placed or single kidney), the longer each step took, and hence, a greater potential for ischaemic injury.

The early animal and clinical studies suggested that 20 minutes of WIT and 120 min of CIT was the safe threshold above which irreversible renal damage was done [26]. This was not universally accepted and others argued that a WIT of up to 30 minutes was acceptable [27]. An elegant combined functional (MAG 3nuclear scan) and anatomical study (CT) from Japan would appear to suggest that the ideal time is around 25 minutes. In this study, Funahashi et al. used functional data from a MAG 3 study to show a net 25% drop in uptake at one week and more crucially that this drop had not recovered by six months. Importantly, the decreased uptake was globally seen and not limited to or concentrated on the operated site [28]. Becker et al. detail an excellent review on the topic of renal ischaemia in partial nephrectomy, which is worth reading as it details the pathophysiology, etc. Basically, the insult comes from a reperfusion injury brought on by free radical release, which, in turn, were formed by adenosine triphosphate breakdown due to vascular endothelial damage. It would also appear that, given that modern OPN is associated with WIT usually below 30 minutes, that there may be no benefit from cold ischaemia or indeed from mannitol. Where used, cold ischaemia is delivered using surface ice slush usually but can also be delivered using a retrogradely placed ureteric catheter or rarely by direct canulation of the renal artery [27].

http://dx.doi.org/10.5772/60543

Given this benchmark WIT of 20–25 minutes, it became crucial that techniques were developed to minimise WIT. The techniques considered were early unclamping, selective clamping or in select cases, control of the artery and vein with manual clamping of the hilum if necessary. This led to an upsurge in laparoscopic partial nephrectomy as the biggest fear amongst those offering LPN was to what extent the prolonged WIT of the early LPN experience had on renal outcomes. In a laparoscopic partial nephrectomy, there are three key steps. The first is lesion excision followed by accurate closure of the tumour bed and collecting system using two layers of interrupted sutures and thirdly, closure of the renal parenchyma. It is the latter that takes most time. Early unclamping is removal of the clamp once the lesion is excised and any repair required to the collecting system is finished. Any bleeding from the tumour bed can be controlled with separate sutures at that time. Nguyen and Gill dropped their WIT from a mean of 31.9 minutes to 13.9 minutes by this simple measure in a series of 100 consecutive LPN. There were more complications in the early unclamping group but this did not reach significance [29]. Similarly, a group from Europe in a cohort of 40 LPN demonstrated an equally impressive reduction in WIT from a mean of 27.2 minutes (± 5) to 13.7 (± 4), where two continuous sutures were used to close the tumour bed before unclamping and 10.3 (± 1.2), where one suture was used. In this study, there were no differences in blood loss, operative time or the need for transfusion between the control and early unclamping groups. Interestingly, the one major urinary leak happened in the control group and unfortunately required nephrectomy for management. The two vascular complications were also in the control group [30].

Selective arterial clamping (with laparoscopic bulldogs) appears to be more commonly studied in the minimally invasive PN series, especially in the robotic partial nephrectomy literature (RPN). The aim is to clamp the second-, third- or fourth-level branches within the renal sinus so that the area of ischaemia is limited to the renal mass only if possible or failing this that the area rendered ischaemic is a small as possible. It requires quite a sophisticated approach, which starts with 3D rendering of the kidney, its tumour and especially, its blood supply. The cross-sectional imaging used for this mapping is most commonly CT but can also be MRI. One- to three-mm slices are taken and processed using software, which provides the 3D reconstruction. The arterial and venous trees can then be mapped from the main artery and vein right up to the lesion. The level of the planned clamping is decided at this time and does not change unless due to unavoidable intraoperative reasons such as unexpected vessels. These images are thus available for review in theatre or in the case of robotic PN can be displayed on the operator's viewscreen.

Suitability for RPN/LPN and the extent of possible complications can be predicted using a variety of nephromotory scoring systems. One of the more commonly used is the Pre-operative Aspects And Dimensions Used for Anatomical (PADUA) system (table 4). It uses six characteristics to classify each lesion. These are relationship to the sinus line, location relative to renal border, relationship to renal sinus, collecting system involvement, the depth of penetration and the lesion size. The minimal score is 6 and the maximal score is 14. Not only can it be used to predict complexity (and thus suitability for PN) but it also correlates with complications. On this basis, lesions can be assigned to one of three groups, Low (6–7), intermediate (8–9) and

Anatomical feature	Scores 1	Scores 2	Scores 3
Sinus line	Entirely polar Crosses line < 50% Crosses > 50%	Between sinus lines	
Location vs. rim	Lateral border Endophytic near lateral border	Medial Border Endophytic near medial border	
Sinus located at lesion	None	Present	
Collecting system involvement	Not involved Dislocated i.e. compressed	Involved	
Depth of penetration into kidney	> 50% Exophytic	< 50% Exophytic	Endophytic
Size of lesion	< 4 cm	4–7 cm	> 7 cm

Table 4. PADUA score

high (>10) risk. Complications are significantly more likely to occur if the score is above 8. Using a baseline score of 6–7 as a comparator, those with a score of 8–9 had a 14-fold increased risk of complications and this increased to a 30-fold increased risk for score > 10 [31].

Shao et al. reported their experience of laparoscopic selective clamping in 125 patients over a two-year period and with 18 months of follow up. Visual clamping of the tumour vessel(s) was achieved in over 90% of cases, with the remainder requiring main artery clamping. The number of vessels clamped was totally dependent on tumour characteristics and this in turn predicted loss of renal function. Clamping of two or more vessels significantly increased the risk of bleeding and reduction in eGFR. Interestingly, they showed that posterior tumours were more likely to require 2 or more vessels clamped. This is slightly surprising given their approach to the kidney is retroperitoneal. Other factors predictive of multiple vessel clamping were size > 3 cm, endophytic lesions or lesions which were < 50% exophytic and lesions which involved both surfaces. Multiple vessel clamping in turn increases renal parenchymal tissue loss and thus renal function [32].

IS Gill is one of the "founding fathers" of PN and has been heavily involved in laparoscopic and robotic renal surgery. He has detailed his experience of LPN and his progression from full clamping through early unclamping, through selective clamping and finally to what he calls "zero ischaemia" [33-34]. This is the ultimate in selective clamping and entails clamping only the lesional vessel. As mentioned above, the preoperative lesional mapping is extremely important and this group uses 2–3 mm slices through the kidney and its vasculature. For their robotic work, the reconstructed images are displayed on the operating surgeons console. Putting this simply, the operating surgeon has a roadmap in front of them as they operate. Not only do they isolate the renal artery and its segmental branches but depending on tumour position, they can dissect third- and fourth-order branches. In addition to the highly detailed roadmap, the visual magnification from the use of MIS and the extra dexterity in tissue

http://dx.doi.org/10.5772/60543

manipulation from using robotic instruments, this group uses two other adjunct techniques to minimise bleeding and clamping. The first was hypotensive anaesthesia. The second is to quantify the ischaemic area using either laparoscopic colour flow doppler ultrasound or more recently, intravenous indocyanine green [34-35].

Hypotensive anaesthesia involved controlled pharmacological lowering of systemic blood pressure. The aim is to avoid vasoconstriction of the arterial tree, thus maintaining perfusion in the setting of low pressure. Initially, the patient is given a mannitol solution followed by preloading with crystalloid. The required MAP of 60 mmHg is reached at the time at which the operator is dissecting the deep part of the lesion. It is achieved using a nitroglycerine infusion and isoflurane inhalation with heart rate support from a short-acting beta blocker. On removal of the lesion, the pressure is reversed. The advantage is that blood loss is minimised by reduced pressure while maintaining tissue oxygenation and thus preventing an ischaemic cascade. The disadvantage is that hypotension may trigger other end-organ failure and result in significant comorbidity. In their later experience, this group no longer used this technique. This is due to a combination of concern regarding the possibility of ischaemic complications such as myocardial infarction or cerebrovascular accidents and improved lesional vascular dissection helped in part by the adjunct technique described below [34-35].

Gill's group now uses indocyanine green as an adjunct to confirm devascularisation. This is used in conjunction with near-infrared fluorescence, which shows a black and white image with perfused areas being bright green. This group place the lesional vascular bulldog clamp. They then intravenously inject 7.5 mg of indocyanine green, switch to near infrared and confirm uptake by visualisation of the renal artery by its being outlined in green following which they visualise the lesion. If it is dark, then super-selective dissection has been successful; if not, they either search for an accessory vessel or convert the procedure to a standard clamped PN [35].

In their pilot study of 34 patients, some 80% underwent zero-ischaemia RPN. Most of the failures were due to persistent fluorescence, indicating accessory vessels. When paired with a cohort of "standard" clamped RPNs, the only differences were a longer operating time and better renal function in the zero-ischaemia group. None of the patients studied had a positive margin [35].

A very interesting by-product of the use of indocyanine green as a marker of devascularisation is that it appears to be poorly absorbed by RCC. Of 10 tumours, seven RCC appears were hypo-perfused, suggesting that this marker may have a further part to play in PN.

The previous ten paragraphs have described some of the techniques and strategies used by those at the cutting edge of partial nephrectomy to marry the enhanced patient experience of MIS with the improved functional outcomes from partial nephrectomy. These trail blazers describe a trifecta for minimally invasive PN of negative surgical margins, minimal loss of renal function and no urological complications. The question to be asked is can similar results be delivered by others.

The more widespread uptake of LPN started when the trail blazing units started to publish their experience. Initially, the lesions treated were the Anterior, polar and exophytic lesions,

which scored a 6–7 using a PADUA system [31]. As experience was gained, units started doing more complicated lesions, while at the same time, experienced open surgeons with some laparoscopy skills began using robotic techniques. To this end, it can be difficult to compare OPN to LPN/ RPN as the number of centres publishing outcome data from LPN/RPN is very small. Amongst others to do such a comparative review was Van Poppel in a publication in 2010 [36]. This review looked at the published data at that time and as such was mainly, but not exclusively, from trail blazing units. The review has multiple tables which, for illustrative purposes, we have, somewhat crudely, condensed into two. The first (Table 5) attempts to summarise the oncological comparison. As would be expected, the mean follow-up is shorter and the mean lesion size is smaller for the LPN group. That said, the immediate (positive margins, local recurrence) oncological measure would appear to be equivalent. The intermediate performance comparator (% 5 year CSS – Cancer Specific Survival) would also suggest LPN provides an equivalent outcome.

	OPN	**LPN**
# Patients per quoted study	51–75	34–430
Mean size lesion (cm)	2.5–5.5	2.9–3.6
% Positive surgical margin	0– 5	0–2.9
% local recurrence	0–5.9	0–2.4
% 5 year CSS	89–98	91–100
% 10 year CSS	76–97	
Mean FU (months)	35–120	15–68

Table 5. Comparison of oncological outcomes of OPN (open partial nephrectomy) and LPN (laparoscopic partial nephrectomy) – modified from Van Poppel [36]

In partial nephrectomy, preservation of renal function and lack of urological complications are equally as important as excellent oncological outcomes. The second of the two tables (Table 6) summarises these outcomes from that Van Poppel publication. Some explanation of the table layout is required. The quoted studies had varying number of patients and hence the wide bands of reported complications. In an attempt to put each complication into context, the cumulative columns were constructed. Thus it can be seen that the operative and functional complications of LPN are equivalent to OPN [36].

One of the concerns expressed about the widespread expansion of LPN/RPN was that WIT times would increase as less experienced surgeons would prioritise tumour excision and renal repair. The accepted optimal WIT has been established at 20-30 minutes [26-28]. However it would appear from the "zero-ischaemia" work quoted above that each minute of WIT increases tissue loss [34-35]. One of the criticisms of MIS is the length of time it takes to become proficiently skilled in the procedure, the so-called learning curve. This is a controversial topic. One definition quoted is the number of cases to achieve a WIT of < 20 minutes. For robotic PN, Mottrie et al. put this at as little as 30–40 cases and based it on a single surgeon experience

http://dx.doi.org/10.5772/60543

	OPN		LPN	
	Range	Cumulative	Range	Cumulative
# Patients per quoted study	59–1029	2756	49–507	1679
% Overall complications	4.1–38.6	587 (21%)	9–33	337 (20%)
% Haemorrhage	0–7.5	88 (3%)	1.5 - 9.5	82 (5%)
% Urine leak	0.7–17.4	109 (4%)	1.4–10.6	57 (3%)
% sepsis	0 - 2.7	13 (0.4%)	0–2.5	11 (0.7%)
% Renal Failure	0–12.7	38 (1.4%)	0–2	12 (0.7%)

Table 6. Comparison of complications of OPN and LPN again modified from Van Poppel [36]

where the mean time for WIT in a group of 10 patients was less than 20 minutes. The caveat to this is that this group had significant robotic experience. However, the editorial comment accompanying their paper appeared incredulous that such a number could be quoted. The author of this editorial had > 400 LPNs under his belt. In LPN, the same debate seems to be taking place [37].

IS Gill suggests that it took him about 550 cases to become what he deemed to be proficient [33]. This is from one of the leading laparoscopic and robotic protagonists of PN. On the other hand, Springer et al. in their paper comparing OPN and LPN state that the fact that the two main surgeons had performed over 90 OPN and LPN each helped overcome the learning curve [38].

Their paper is worth summarising, representing as it does the experience of an early adapter of LPN where previously OPN was the procedure of choice. This group compared 140 consecutive LPNs (May 2005–November 2010) to a historic control group of 140 OPN (May 1999–April 2005). Overall, the oncological results, both in terms of positive margins (1.2 % LPN, 1.7 % OPN) and five-year CSS (91% LPN, 88% OPN), were identical and identical to the review by Van Poppel, which is tabulated above [36]. In addition, the functional outcomes were identical with approximately 5% of each group having post-operative complications. Hence, it would appear that the excellent results from LPN performed at centres of excellence are transferrable to the wider urological community.

This may be a moot point because of the rapid expansion in centres offering RAPN. Primarily, this is because robotics offers several significant advantages over "traditional" LPN. These are improved magnification, greater surgeon ergonomic comfort, instruments such as the endoWrist, which give greater degrees of movement facilitating easier dissection and suturing [35-37]. One of the latest meta-analyses on series comparing LPN and RPN is from Zhang et al. They identified seven valuable studies from an initial find of 569 studies on the topic. Unsurprisingly, there was no difference in tumour characteristics nor indeed in any discussed parameter apart from WIT. This was significantly shorter in the RAPN groups. While this is not a new finding, it is not universally found. It does appear to reaffirm the fears about LPN being associated with prolonged WIT. Looking at the tables in a little more detail, it becomes apparent that the series with larger numbers tended to have identical and more acceptable

	RPN		LPN	
	Ranges	**Cumulative**	**Ranges**	**Cumulative**
Numbers in quoted studies	11–220	425	14–102	341
Mean operating time in mins	152.17–233	176.2	117.5–226.5	194.35
Mean WIT mins	14.1–35.3	19.83	17.2–36.4	41.9
Mean blood loss mls	122.4–286.4	239.51	146.3–387.5	232.31
Conversion rate	N = 0–13 (0- 5.9%)	N = 18 4.24%	N = 0–5 (0–15%)	N = 12 3.52%
Positive margins	N = 0–18	N= 22 5.58%	N = 0–7	N = 11 3.49%
Complications	N= 0–45 (0–22%)	N = 69 (17.51%)	N= 0–17 (0–31%)	N = 55 (16.92%)
LOS days	2.51–6.1	4.98	2.7–6.8	4.48

Table 7. Comparison of complications and immediate oncological outcomes of RAPN (Robotic assisted) and LPN (Laparoscopic), modified from Zhang et al. [39] N refers to the total number of patients in the studies quoted

WIT for both RAPN and LPN. If 21 minutes is used as a marker for an acceptable WIT limit, four of the LPN and two of the RAPN trials are well above that limit. This is not discussed in the review but it may represent a learning curve effect or may reflect surgeons switching to the technically less demanding robotic approach [39]. Some evidence, albeit circumstantial, for the latter point is that having access to robotic technology increases the uptake of PN [40].

As can be seen from the preceding tables, it can be difficult to compare the MIS techniques for PN. In an effect to standardise reporting of outcomes, the MIC system was proposed and some groups have reanalysed their data accordingly. The MIC system is based on the trifecta discussed earlier. That is, negative surgical margins, WIT < 20 minutes and no significant complications. MIC is present when all three factors are present. Acceptability in terms of a study is where the global MIC score is > 80%. In their study, Porpiglia et al. showed increasing MIC with increasing experience and that acceptability was achieved after approximately 150 cases of LPN, i.e. the learning curve is 150 cases. The other factor negatively affecting MIC was increasing complexity of cases [41].

The future of endoscopically delivered NSS is secure and judging by recent publications describing MIS PN for increasingly more complex lesions, the focus will shift to which technique will become most practised. The debate is no longer about whether OPN is superior, it is now how about which of the endoscopic techniques will best achieve MIC.

4. Renal ablative therapies

Whilst most groups focused on organ preservation through PN other looked at the role of ablative technologies. The European Association of Urology guidelines suggest ablative

http://dx.doi.org/10.5772/60543

therapies can be used for High risk patients who are keen to have definitive treatment. Two ablative techniques have entered main stream clinical practice and these are radiofrequency ablation (RFA) which uses heat energy and Cryotherapy (CA) which uses cold energy applied in a heat–thaw cycle to produce cell death. Tissue destruction happens when sufficient energy is applied at a rate equal to the rate thermal energy is removed (i.e. Heat sink). These techniques can be performed under general anaesthesia or sedation and in either an operating theatre (using ultrasound as the image guidance technique) or interventional radiology suite (using CT or MRI). Both require intensive imaging-based follow-up schedules as post-ablative biopsy histology is not very accurate. Failure (persistent contrast enhancement or growth on serial scans) or success (no contrast enhancement, lesion shrinkage) is based on cross-sectional imaging findings [42].

4.1. Cryotherapy Ablation (CA)

Cryotherapy has primarily been delivered laparoscopically. The principle is to deliver sufficient energy using freeze–thaw cycles to cause apoptosis and cell damage by mechanical and vascular means. The initial freeze cycle (using Argon gas) causes ice formation within the extracellular spaces. This acts as an osmotic agent and attracts fluid from the intracellular space. Freezing also causes mechanical cell damage. Thawing (using Helium gas) restores blood flow but damaged cells are released into the vasculature and result in thrombosis. The ideal freeze time appears to be 10 minutes for RCC based on basic science and clinical studies. The ideal tissue temperature is approximately -40^0C. The margin of the iceball should be approx. 0.5 cm beyond the rim of the lesion [42].

Most of the studies on CA for localised RCC have involved a large proportion of small lesions < 3 cm and have at best short- to medium-term follow-up. The majority have performed laparoscopically. The initial oncological results seem encouraging with reported 3- and 5-year CSS equivalent to that of PN AT 98–100% and 92%, respectively. The downside is that there is a significant local failure rate of 10–20%. Aron et al. have 5-year follow-up on a group of 80 patients. Their 5-year CSS is 92% but the local recurrence rate is 14%. The definition of recurrence post CA is radiological because of the difficulty interpreting post CFA biopsy specimens. Exophytic, small (<3 cm) lesions along the lateral rim of the kidney are those with the best outcomes [43].

While CA appears to be an effective therapy, there are very few head-to-head trials comparing it to PN. One such trial was conducted by Tanagho et al., who compared CA to RAPN. This trial used the Clavien classification of complications, which standardises definitions and allows for more accurate reporting. Many criticisms of LCA trials had discussed complication reporting in addition to a more favourable lesional profile. They compared 267 patients treated by CA to 233 RAPN and the groups were matched for all matched characteristics. The immediate complication rate was equal (CA 8.6% vs. RAPN 9.4%). The renal preservation was significantly better for CA, but this was at the cost of a 12.7% local recurrence rate at approx. 40 months versus 0% for RAPN at a mean fu of approximately 22 months. That said, they conclude that CA is an excellent therapy [44].

4.2. Radio Frequency Ablation (RFA)

This is predominantly delivered percutaneously. A probe is advanced under screening into the lesion and heating begun using a high-frequency alternating current. This induces molecular oscillation, which leads to friction and cell death by coagulative necrosis. The temperature at the centre of the lesion lies between 50 and 120 °C depending on the interplay between device and patient factors. Device factors include the probe composition, its surface area, length and duration of use. Patient factors include the position of the lesion vis-à-vis the hilum (i.e. collecting system and major vessels), which can affect the heat sink principle as proximity to a major vessel results in greater heat dissipation, which in turn leads to less thermal injury to the lesion unless more energy is delivered. Depending on the tissue temperature, the destruction can be instantaneous or result in the triggering of an inflammatory cascade [42].

A recent report on 200 RFA in 165 patients is one of the largest to date and is unusual in that most of the treatments were performed under general anaesthesia. This may explain the technical success rate of 98.5% in a group of lesions of mean size 2.9 cm (range 1–5.6). For central lesions, they used cold pyeloperfusion to cool the upper ureter and collecting system via a retrogradely placed ureteric catheter. They also describe hydrodissection to move bowel within 1 cm of an exophytic lesion. This is achieved by the instillation of dextrose solution (i.e. nonconductive).

In terms of oncological outcomes, this group achieved a 97.9% CSS with exophytic and tumours < 3 cm doing best. Nine required retreatment and of those, six were tumour free after a further 1–2 treatments. From a functional outcome, Only 2% of their cohort had long-term renal function loss [45].

5. Conclusion

Open Radical Nephrectomy has gone from being the only therapy available to treat localised RCC to a therapy which is now rarely practised. Indeed, partial nephrectomy seems to be competing with ablative therapies for localised disease. This chapter has attempted to trace that change albeit trying to simplify the often crossing timelines between the various interventions. The place of endoscopy in organ preservation in localised RCC is however secure.

Author details

J.G. Calleary*, T. Lee, B. Burgess, R. Hejj and P. Naidu

*Address all correspondence to: johngcall@aol.com

Department of Urology, Pennine Acute Hospitals, North Manchester General Hospital, Crumpsall, Manchester, UK

http://dx.doi.org/10.5772/60543

References

[1] BLUS handbook of Laparoscopic and Robotic fundamentals. http: // www.aua.org/common/pdf/education/BLUS-Handbook-pdf accessed Jan 15th 2015

[2] Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol 1969;101: 297–301.

[3] Chatterjee S, Nam R, Fleshner N, Klotz L. Permanent flank bulge is a consequence of flank incision for radical nephrectomy in one half of patients. Urol Oncol 2004 Jan-Feb; 22(1): 36-39.

[4] Clayman RV, Kavoussi LR, Soper NJ. et al. Laparoscopic Nephrectomy: initial case report. J Urol 1991; 146(2): 278-282.

[5] Dunn MD, Portis AJ, Shalhav AL, Elbahnasy AM, Heidorn C, McDougall EM, Clayman RV: Laparoscopic versus open radical nephrectomy: a 9-year experience. J Urol 2000; 164:1153-1159.

[6] Pareek G, Hedican SP, Gee JR, et al. Meta-analysis of the complications of laparoscopic renal surgery: comparison of procedures and techniques. J Urol. 2006;175(4): 1208-1213.

[7] Xu H, Ding Q, Jiang HW. Fewer complications after laparoscopic nephrectomy as compared to the open procedure with the modified Clavien classification system--a retrospective analysis from southern China. World J Surg Oncol. 2014 Jul 31;12:242.

[8] Luo JH, Zhou FJ, Xie D, et al. Analysis of long-term survival in patients with localized renal cell carcinoma: laparoscopic versus open radical nephrectomy. World J Urol 2010; 28(3): 289-293.

[9] EAU guidelines. http: //www.uroweb.org/gls/pdf/10_Renal_Cell_Carcinoma_LR.pdf (accessed Jan 15th 2015).

[10] Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. JNCI Sep 20, 2006; 98(18):1331–1334.

[11] Chow WH, Devesa SS, Warren JL. et al. Rising incidence of renal cell cancer in the United States. *JAMA* 1999; 281(17):1628-1631.

[12] Go AS., Chertow GM., Fan D, McCulloch CE & Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med* 2004; 351: 1296–1305.

[13] Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol. 2006 Sep; 7(9):735–740.

[14] Novick AC. Renal Hypothermia: in vivo and ex vivo. Urol Clin North Am 1983; 10:637-644.

[15] Kim, SP. *et al.* Contemporary trends in nephrectomy for renal cell carcinoma in the United States: results from a population based cohort. J. Urol. 2011;186: 1779–1785.

[16] Lau WK, Blute ML, Weaver AL, Torres VE, Zinke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc 2000; 79(12): 1236-1242.

[17] Tan HJ, Norton EC, Ye Z, Hafez KF, Gore JL, Miller DC. Long-term survival following partial versus radical nephrectomy among older patients with early-stage kidney cancer. JAMA 2012 April 18; 307(15).

[18] Yossepowitch O, Thompson RH, Leibovich BC *et al.* Positive surgical margins at partial nephrectomy: predictors and oncological outcomes. J. Urol. 2008; 179: 2158–2163.

[19] Van Poppel H, Joniau S. How important are surgical margins in nephron-sparing surgery? Eur. Urol. Suppl 2007; 6: 533–539.

[20] Minervini A, Tuccio A, Lapini A. *et al.* Review of the current status of tumor enucleation for renal cell carcinoma. Arch. Ital. Urol. Androl. 2009; 81: 65–71.

[21] Badalato GM, Kates M, Wisnivesky JP, Choudhury AR, McKiernan JM. Survival after partial and radical nephrectomy for the treatment of stage T1bN0M0 renal cell carcinoma (RCC) in the USA: a propensity scoring approach. BJUI 2011; 109: 1457-1462.

[22] Matin SF[1], Gill IS, Worley S, Novick AC. Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4 cm. or less renal tumor with a normal contralateral kidney. J Urol. 2002 Oct; 168(4 Pt 1):1356-1359; discussion 1359-1360.

[23] Lesage K, Joniau S, Fransis K, Van Poppel H. Comparison between open partial and radical nephrectomy for renal tumours: Perioperative outcome and health-related quality of life. Eur Urol 2007; 51: 614–620.

[24] NCI dictionary of cancer terms. Accessed on Jan 15th at www.cancer.gov/dictionary?cdrid = 630927.

[25] Gill IS. Towards the ideal partial nephrectomy. Eur Urol 2012: 62(6); 1009-1010.

[26] Simmons MN, Schreiber MJ, Gill I. Surgical renal ischemia: a contemporary overview. J Urol 2008; 180:19–30.

[27] Becker F[1], Van Poppel H, Hakenberg OW. et al. Assessing the impact of ischaemia time during partial nephrectomy. Eur Urol 2009 Oct; 56(4):625-634.

[28] Funahashi Y, Hattori R, Yamamoto T. et al. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. Eur Urol 2009; 55(1): 209-215.

[29] Nguyen MM, Gill IS. Halving ischemia time during Laparoscopic Partial Nephrectomy. The Journal of Urology 2008 ;179(2): 627-632.

[30] Baumert H, Ballaro A, Shah N. et al. Reducing warm ischaemia timeduring Laparoscopic Partial Nephrectomy: A prospective comparison of two renal closure techniques. Eur Urol 2007: 52; 1164–1169.

[31] Ficarra V, Novara G, Secco S, Macchi V. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nNephron-sparing surgery. Eur Urol 2009; 56(1): 786-793.

[32] Shao P, Tang L, Pu L. et al. Precise segmental renal artery clamping under the guidance of dual-source computed tomography angiography during laparoscopic partial nephrectomy. Eur Urol 2012, 62, 1001-1008.

[33] Gill IS, Kamoi K, Aron M, Desai MM. 800 Laparoscopic partial nephrectomy: a single surgeon series. J Urol 2010; 183: 34–41.

[34] Gill IS, Eisenberg MS, Aron M. et al. "Zero ischemia" partial nephrectomy: novel laparoscopic and robotic technique. Eur Urol 2011 Jan; 59(1):128-134.

[35] Borofsky MS, Gill IS, Hemal AK. et al. Near-infrared fluorescence imaging to facilitate super-selective arterial clamping during zero-ischaemia robotic partial nephrectomy. BJU Int 2013 Apr; 111(4): 604-610.

[36] Van Poppel H. Efficacy and safety of nephron-sparing surgery. International Journal of Urology 2010; 17, 314–326.

[37] Mottrie A, De Naeyer G, Schatteman P. et al. Impact of the learning curve on perioperative outcomes in patients who underwent robotic partial nephrectomy for parenchymal renal tumours. Eur Urol 2010; 58: 127-133. Discussion 133.

[38] Springer C, Hoda MR, Fajkovic H. et al. Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients. BJUI 2012; 111: 281-288.

[39] Zhang X, Shen Z, Zhong S. et al. Comparison of peri-operative outcomes of robot-assisted vs laparoscopic partial nephrectomy: a meta-analysis. BJUI 2013; 112: 1133-1142.

[40] Kardos SV, Gross CP, Shah ND. et al. Association of type of renal surgery and access to robotic technology for kidney cancer: results from a population-based cohort. BJUI 2014; 114: 549–554.

[41] Porpiglia F, Bertolo R, Amparore D, Fiori C. Margins, ischaemia and complications rate after laparoscopic partial nephrectomy: impact of learning curve and tumour anatomical characteristics. BJUI 2013; 112: 1125–1132.

[42] Ramanathan R. Leveillee RJ. Ablative therapies for renal tumors. Ther Adv Urol 2010; 2(2): 51-68.

[43] Van Poppel HV, Becker F, Cadeddu et al. Treatment of localised Renal Cell Carcinoma. Eur Urol 2011; 60: 662–672.

[44] Tanagho YS, Bhayani SB, Kim EH, Figenshau RS. JEndourol 2013; 27(12): 1477-1486.

[45] Wah TM, Irving HC, Gregory W. et al. Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. BJUI 2013; 112 (3): 416 – 428.

Chapter 18

Endoscopic Management of Pediatric Airway and Esophageal Foreign Bodies

Phillip L. Chaffin, Jonathan M. Grischkan,
Prashant S. Malhotra and Kris R. Jatana

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60590

Abstract

The use of endoscopy is critical to the management of pediatric tracheobronchial and esophageal foreign bodies. Children may present with nonspecific symptoms, and the diagnosis can be difficult when the ingestion or aspiration events go unwitnessed. Advances in endoscopic techniques and the use of optical graspers in the removal of foreign bodies in children have helped decrease morbidity and mortality. In this chapter, the history, clinical presentations, workup, and management for pediatric aerodigestive foreign bodies are discussed.

Keywords: foreign body, pediatric airway, esophagus, endoscopic, aspiration, ingestion

1. Introduction

The history of endoscopic management of pediatric foreign bodies was predated by significant innovations allowing for the evolution of adult and pediatric bronchoesophagology. Prior to these advances, tracheotomy was the accepted method for successful removal of airway foreign bodies [1]. In 1806, Philipp Bozzini, reported using the "lichtleiter" or "light conductor" to visualize the upper esophagus using candle illumination [2]. While his instruments and methods did not gain wide acceptance during his lifetime, they set the stage for further innovations that occurred over the ensuing decades. Desormeaux, a urologist, is credited with coining the term "endoscopy" in 1867 [3] and is considered by most to be the "Father of

Endoscopy" [4]. Kussmaul is credited with performing the first direct esophagoscopy, and his student Killian further explored these techniques and instrumentation. Mikulicz further refined the techniques and instrumentation of esophagoscopy, bringing it into more common use [5].

In 1895, Alfred Kirstein, a laryngologist in Berlin who was familiar with the work of Kussmaul and Mikulicz, was the first to directly visualize the larynx and trachea [6]. Killian became interested in Kirstein's achievements and began to practice laryngoscopy on cadavers and tracheotomized patients. In 1897, he was the first to remove a foreign body from the right mainstem bronchus of an adult via the translaryngeal route. His contributions and achievements have prompted many to consider him the "Father of Bronchoscopy" [7]. Following these innovations, tracheoscopy and bronchoscopy became accepted surgical techniques.

Chevalier Jackson became interested in laryngology while studying medicine in Pennsylvania and eventually furthered his studies in London. After learning the techniques of his mentors and as an instrument maker, he created an esophagoscope allowing for direct visualization of the esophagus. With this design, he was successful in removing esophageal foreign bodies from both adults and children. Jackson further refined his technique and the instruments he used, eventually developing the largest endoscopy clinic in the world [5]. Through the innovations of Jackson and his predecessors, the techniques for removal of esophageal and airway foreign bodies was perfected, reducing the mortality from foreign body ingestion or aspiration from more than 50% to less than 2% [5].

2. Endoscopic equipment

Modern endoscopic equipment is available in various sizes and configurations to accommodate patient age and size, and the use of flexible vs. rigid endoscopic equipment are both available (Figure 1). There are some clear advantages to the use of rigid bronchoscopy for removal of a tracheobronchial foreign body. The scope is designed to have ventilating ports so the anesthesia circuit can be directly attached for active ventilation and control of the airway during the procedure.

Flexible bronchoscopy can be done with insufflation techniques in the oropharynx or through the scope, but the channel on the scope is small, thus limiting flow of gas. Alternatively, the flexible scope can be passed through a secured endotracheal tube (Figure 2). If the foreign body cannot fit through the endotracheal tube, then this creates a problem for removal with the tube in place. The foreign body forceps have more limited sizes with flexible bronchoscopy, and there is also less control of the scope itself since it can bend to various configurations. Certainly in our experience, flexible bronchoscopy can be a useful adjunct to removal of foreign bodies, as it can give more distal visualization of the lower airways for small food particles, like nuts, that may fall further than the rigid scopes can reach. Such smaller, distal airways can be irrigated with saline and additional attempts using flexible or rigid bronchoscopy can then be utilized to remove these small fragments using endoscopic optical graspers or suction.

http://dx.doi.org/10.5772/60590

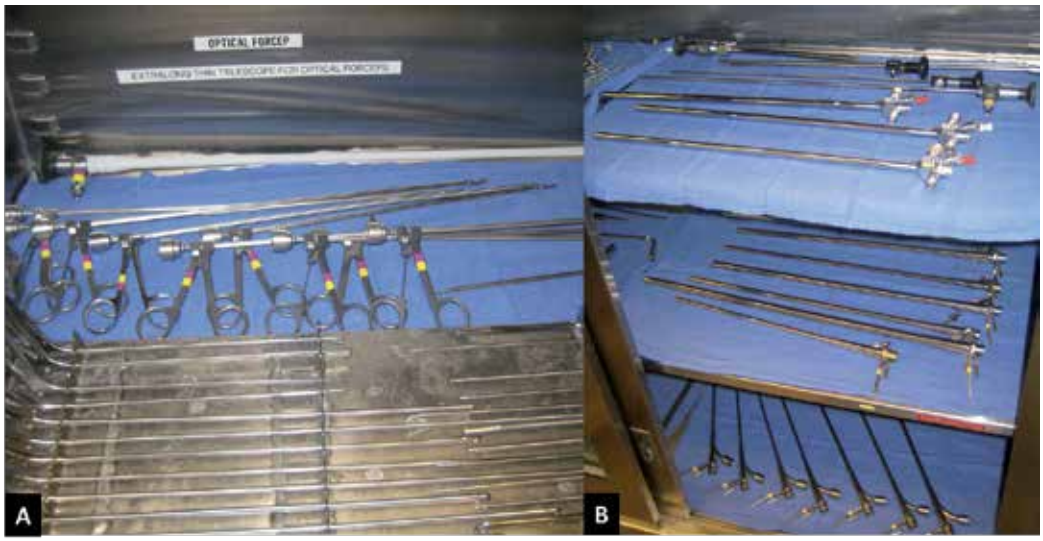

Figure 1. A) Various non-optical and optical graspers used for removal of foreign bodies from the aerodigestive tract. B) Rigid, ventilating bronchoscopes of various sizes. Selection depends on the age of the patient and size of the airway.

Figure 2. Flexible bronchoscopy cart setup.

For esophagoscopy, the use of the rigid scope allows for use of the same endoscopic optical graspers used in airway cases. While many esophageal foreign bodies are safely removed with flexible endoscopy, the rigid scope does not require insufflation of the esophagus with air and using rigid equipment, more direct visualization of the insertion through the upper esophageal sphincter can be made. There are fewer options for types of graspers available for the flexible esophagoscope. In our opinion, the endoscopic optical graspers themselves used through the rigid scope allow for enhanced visualization and easier foreign body removal (Figure 3).

Figure 3. An example of an endoscopic, optical coin grasper, with a fine tooth at the tip, which allows the coin to pivot or swivel through the path of least resistance through the esophagus during removal.

3. Relevant airway anatomy

The upper aerodigestive tract extends from the lips and nasal vestibule to the upper esophagus and trachea and mainstem bronchi. It can be divided into anatomic subsites, including the nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, trachea, bronchi, and esophagus.

With regard to the nasal cavity, foreign bodies typically get lodged between the inferior turbinate and the septum. As the nasal cavity is part of the airway, care must be taken during removal attempts in the office setting to avoid converting this upper airway foreign body into a lower airway foreign body.

Several differences between the adult and pediatric airway exist that the endoscopist should consider when evaluating and treating patients with aerodigestive foreign bodies. First, the infantile larynx is positioned much higher in the neck. Additionally, the neonatal larynx is

http://dx.doi.org/10.5772/60590

approximately one-third the size of the adult larynx, with the narrowest portion being at the level of the cricoid cartilage and not at the level of the glottis, as in adults [8]. A small reduction in the size of the pediatric airway can have significant and devastating consequences. The size of the airway must be kept in mind when choosing the appropriate size of the bronchoscope. As a general rule, the largest size ventilating scope that can be placed based on age of the child and size of subglottis, allows for optimal ventilation, visualization, and endoscopic removal.

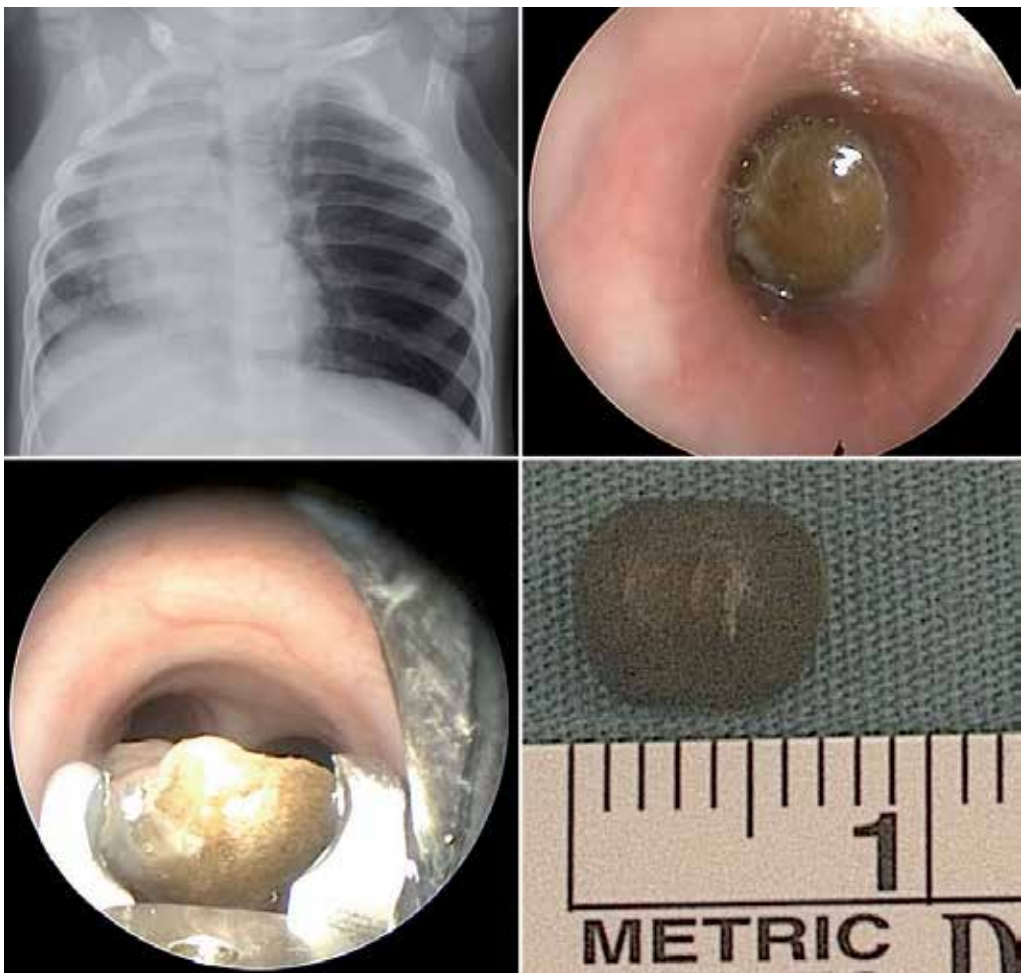

Figure 4. A 13-month old presented to the emergency room with wheezing and coughing. The child had reportedly put something into its mouth earlier that day. An A-P plain film showed hyperinflation of the left lung with right-sided mediastinal shift. There was no radiopaque foreign body noted on the plain film. Direct laryngoscopy with rigid bronchoscopy revealed a left mainstem foreign body, consistent with half of a wooden bead that was removed with an endoscopic optical forceps.

The presence of a foreign body within the tracheobronchial tree can lead to a ball-valve effect, resulting in early hyperinflation of the lung ipsilateral to the foreign body (Figure 4). Over

time, the obstructed lung segment becomes atelectatic. In addition to its physical obstruction, the presence of a foreign body disrupts the normal mucociliary clearance of the tracheobronchial tree. These factors can contribute to the rapid accumulation of secretions and subsequent superimposed pneumonia [9].

The right mainstem bronchus creates a more obtuse angle with the trachea when compared to the left mainstem bronchus, leading to a higher incidence of right-sided airway foreign bodies [10].

4. Relevant esophageal anatomy

There are several anatomic considerations that can lead to arrested passage of an esophageal foreign body through the digestive tract and into the stomach. These sites include the upper esophageal sphincter or cricopharyngeus, the mid-esophagus where the aortic arch crosses, and the lower esophageal sphincter. Additionally, there are a few pathologic conditions that can predispose pediatric patients to dysphasia and esophageal foreign bodies, including vascular rings and slings.

5. Pediatric airway foreign bodies

5.1. Epidemiology

Airway foreign bodies represent an important cause of pediatric morbidity and mortality both in developed and developing countries. According to the US CDC's Morbidity and Mortality Weekly Report, nonfatal choking-related episodes among children less than 14 years old were responsible for approximately 17, 000 emergency room visits in the year 2001 alone, with an estimated rate of 29.9 episodes per 100, 000 children. The incidence was greatest in patients less than 1 year old (140.4 per 100, 000) and steadily declined with increasing age. Seventy-seven percent of patients presenting with chocking-related symptoms were three years old or younger. In their data, there was a higher incidence in males (55.1%) and a higher incidence of food-related substances when compared to nonfoods (59.5% vs. 31.4%, 9% unknown) [11]. The most commonly aspirated foreign bodies include round, hard foods such as nuts, seeds, beans, corn, and berries [12].

In Tan et al.'s 10-year retrospective review of children treated for airway foreign bodies via bronchoscopy, they reported a male preponderance (63.7%) in a series of 135 cases. Three quarters of their patients were under 3 years of age [13]. Both of these trends mirror that of other published series [14–16]. Tan proposed that the higher incidence of foreign body aspiration in younger children was due to their poor oro-motor control and their lack of dentition, in addition to their propensity to explore the world with their mouths.

Prior to the advent of modern endoscopic techniques, the reported mortality from aspirated foreign bodies was as high as 50% or greater [5]. Following the advent of endoscopic techniques

http://dx.doi.org/10.5772/60590

and increased public awareness, the mortality rate of patients with foreign bodies is approximately 1% [17]. The total number of foreign body--related deaths in the United States is estimated to be between 500 and 2000 [13].

The nasal cavity is the most common sub-site for foreign bodies when considering the entire upper aerodigestive tract, accounting for approximately two-thirds of all foreign bodies. In Chinski's study of aerodigestive tract foreign bodies in Argentina, 1559 nasal foreign bodies were reported. The most common objects found in the nose in decreasing order were pearls, stationery, food, seeds/nuts/beans, pins/nails/metal, other inorganic materials and stones, followed by other less common items, including 1 button battery and 11 magnets [18]. The majority of nasal foreign bodies occur on the patient's right side, with this trend increasing with the patient's age [19]. Interestingly, some studies have demonstrated a decreased incidence of nasal foreign bodies during the summer months [20]. Others have commented on the increased incidence of nasal foreign bodies during the months of January, March, April, and October, coinciding with the months near Christmas, Easter, and Halloween when children are exposed to more toys and treats [19].

5.2. Clinical evaluation

5.2.1. Nasal foreign bodies

Many nasal foreign bodies are asymptomatic, presenting only because their placement was witnessed or admitted (Figure 5). Unwitnessed or untreated nasal foreign bodies may present with a variety of symptoms, including unilateral purulent rhinorrhea or nasal obstruction, halitosis, epistaxis, sinusitis, or a combination of these symptoms [19, 21]. A nasal septal hematoma should be differentiated from a nasal foreign body (Figure 6). In a European study assessing complications and hospitalizations due to nasal foreign bodies, Gregori et al. demonstrated that battery nasal foreign bodies were more likely to experience complications and require hospitalizations when compared to many other types of nasal foreign bodies [21]. As with other studies regarding aerodigestive foreign bodies, they reported a fairly high incidence of children placing nasal foreign bodies while under adult supervision (38%).

5.2.2. Laryngeal and tracheobronchial foreign bodies

Foreign bodies of the laryngotracheobronchial tree can present with varying degrees of airway symptoms depending on their location, shape, size relative to airway, and chronicity.

Larnygeal Foreign Bodies

Foreign bodies of the larynx, while infrequent, are associated with the most devastating outcomes. In addition to more common symptoms associated with foreign bodies of the trachea and bronchi, these patients are more likely to present with hoarseness, aphonia, drooling, stridor, and drooling. Complete obstruction can cause cyanosis, respiratory distress, and respiratory arrest followed by death. Persistent irritation can lead to significant laryngeal edema that can persist and cause significant symptoms even after foreign body removal [10, 22].

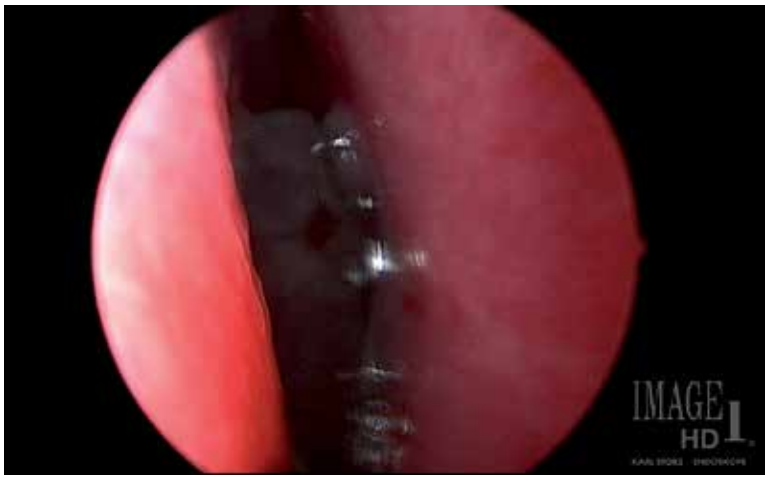

Figure 5. Right nasal foreign body, a piece of broken glass, placed by a 5-year old boy. This was removed in the operating room, instead of clinic setting, due to sharp edges and risk of bleeding following removal.

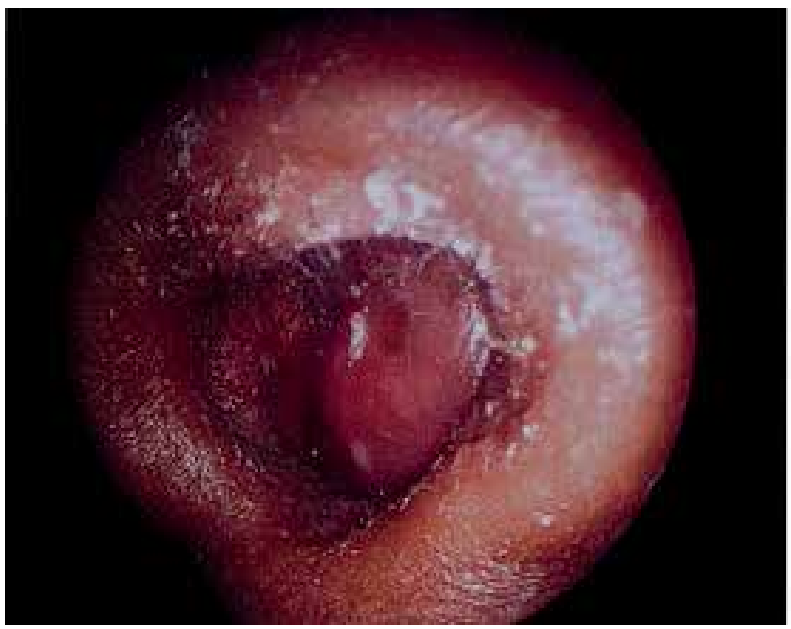

Figure 6. Right nasal septal hematoma after nasal trauma could be mistaken for a foreign object; the mucoperichondral flap is fluctuant to palpation with a cotton tip applicator. Surgical drainage is the required treatment to prevent abscess formation and cartilage necrosis.

Tracheal Foreign Bodies

Patients with tracheal foreign bodies may present with biphasic stridor, a dry cough with an associated "sharp crack" or "slap" when a moving foreign body impacts the subglottis. Patients

http://dx.doi.org/10.5772/60590

may place themselves in the "tripod" position, leaning forward with elbows or hands on their knees. There may also be a dramatic shift in symptoms when the patient changes positions, owing to the mobility of the foreign body [22].

Bronchial Foreign Bodies

In Tan et al.'s series, the most common presenting symptoms of tracheobronchial foreign bodies were "choking, coughing, gagging" with 91.8% of patients presenting in this manner. This was followed by "wheezing" in 84.4% of patients and finally the classic triad of "coughing, wheezing, and reduced breath sounds" in only 57% of patients. Less common symptoms reported in their series included fever, pneumonia, stridor, chest pain, blood stained mucous, restlessness, throat discomfort, sternal discomfort, increased seizure episodes, and nose bleed [13].

5.3. Radiographic evaluation

A thorough history and physical exam are paramount in the evaluation of a child with suspected foreign body and can frequently lead to a diagnosis without the need for further diagnostic workup or imaging. Traditionally, plain film radiography has been advocated for patients with suspected foreign body aspiration. A-P and lateral plain films may reveal a radiopaque foreign body within the tracheobronchial tree. Additionally, sequelae from the presence of the foreign body may be recognized, including air-trapping with associated mediastinal shift, atelectasis, or pneumonia from long-standing foreign body. Decubitus films may demonstrate lack of dependent mediastinal shift on the side ipsilateral to the foreign body [23].

The use of plain film radiography does not need to be routinely employed in patients where there is a high index of suspicion for foreign body based on history and physical examination. In a 6-year retrospective review of 93 cases of possible airway foreign body cases, Silva et al. reported a imaging study sensitivity and specificity of 74% and 45%, respectively [24]. In a series of 232 patients with pre-operative radiography in whom foreign bodies confirmed via bronchoscopy, 110 had plain film imaging that was considered normal by the surgeon (47%). For patients with radiology reports, 42% of patients with bronchial foreign bodies and 81% of patients with tracheal foreign bodies had negative imaging reports. The same study did note that patients with long-standing foreign bodies are more likely to have positive findings on plain film radiography when compared to patients with foreign bodies that have been present for less than 24 h [25]. In their retrospective reviews, neither Assefa nor Brown found sufficient evidence to support the routine use of decubitus films in the identification of airway foreign bodies, citing the lack of sensitivity [23, 26].

Some studies have reported on the diagnostic utility of CT imaging and CT virtual bronchoscopy, with reported sensitivities and specificities ranging from 90% to100% [27, 28]. Foreign bodies that are radiolucent on plain films may be identified on CT. The risks of ionizing radiation and the inability to concurrently diagnose and treat foreign body aspiration should be recognized when considering these modalities.

Despite negative imaging studies, if the history is concerning for possible aspiration, then endoscopic evaluation should still be considered given the potential morbidity and mortality of airway foreign bodies.

5.4. Airway foreign body removal

Nasal foreign bodies can frequently be managed in the clinic if the object is in the anterior nasal cavity. After removal, confirmation using nasal endoscopy can ensure that no additional retained foreign body is present. Objects that are difficult to grasp or that are posterior within the nasal cavity may require sedation or a general anesthetic removal. If the object is round, using a right angle probe behind it and pulling anterior is safest, to avoid propelling the object into the pharynx or causing it to be aspirated into the lower tracheobronchial tree. Other upper airway foreign bodies require direct laryngoscopy and removal with endoscopic visualization of the pharynx and larynx (Figure 7). These are considered an emergency as they can potentially lead to lower airway obstruction if the object is aspirated. When done in the operating room, the endoscopist must be prepared for emergent bronchoscopy, should the object fall distally during induction of anesthesia. Thorough discussion with the anesthesia team on the plan prior to induction must take place. All potential non-optical and optical graspers should be available to quickly use as needed. In addition, instrumentation for emergent tracheostomy placement should be immediately available should the need arise. Figures 8-14 demonstrate a variety of cases where endoscopic management was performed.

5.4.1. Anesthetic considerations

The choice of anesthetic technique should be based on a discussion between the surgeon and anesthesiologist. Pediatric airway and esophageal foreign body removal is performed under general anesthesia. Anesthetic induction can be achieved either by inhalation of volatile anesthetic gas or intravenous medications. Anesthesia can then be maintained with spontaneous ventilation or paralysis with control of the airway. This choice is surgeon and anesthesiologist dependent, but should be agreed upon prior to the start of the procedure.

Especially in the case of tracheobronchial foreign bodies, constant and deliberate communication regarding the airway should be maintained between the surgical and anesthesia teams. This situation represents a true “shared airway”[29, 30].

An age-appropriate size bronchoscope and one size smaller should always be set up for tracheobronchial foreign bodies. A back-up fiberoptic light source is helpful in case one fails during the procedure. Given that the rigid bronchoscope itself is a means of ventilation, strategic use of the instrument during the procedure is important. For example, if the oxygen saturations drop, the telescope can be removed and this increases the ventilating diameter, and therefore the volume of airflow through the bronchoscope tube with occlusion of the proximal end with a cap. The mouth and nose can be manually sealed around the scope to create some “positive pressure” as needed. Optical graspers of various shapes can be easily passed through the bronchoscope while maintaining ventilation, and foreign bodies can be removed under direct endoscopic visualization. The surgeon must ensure all equipment is

http://dx.doi.org/10.5772/60590

functional, available, and all desired instruments fit through the bronchoscope size selected prior to the patient's anesthetic induction.

Tracheostomy is rarely required; however, equipment should be immediately available for obtaining an emergent surgical airway in the management of airway foreign bodies. This is always discussed with the parents during the informed consent process.

5.4.2. Adjunctive procedures

In the rare case where the foreign body cannot be removed endoscopically, additional interventions may be required. As a temporizing measure, the use of extracorporeal membrane oxygenation (ECMO) may allow oxygenation in a case of inability to ventilate [31]. This is a highly specialized technique that is not available in all centers. It allows oxygenation of the blood and maintenance of circulation until a definitive plan for removal can be facilitated.

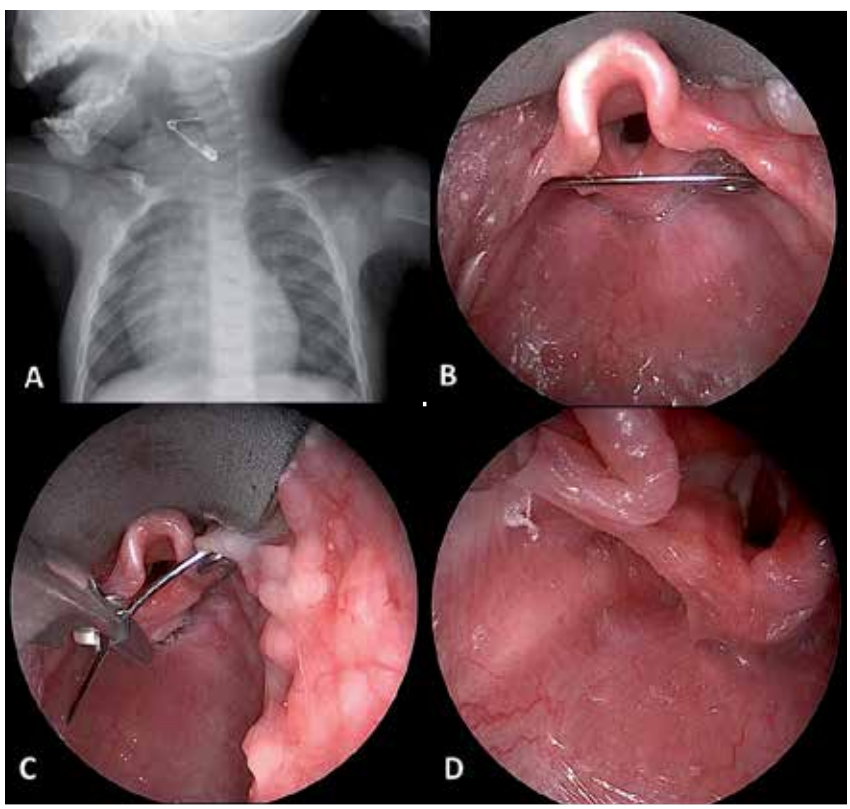

Figure 7. An 11-month old with an open safety pin in the upper airway. The patient presented with irritability and drooling of several hours duration, and the mother felt the child might have put something into its mouth. A-P and lateral plain films confirmed the diagnosis.

In cases where the foreign body cannot be removed endoscopically, open approaches may be required [32]. Cervical esophagostomy for proximal esophageal foreign bodies, or thoracoto-

my with bronchotomy, may be required for tracheobronchial foreign bodies. In these rare cases, close collaboration with pediatric thoracic surgeons or pediatric surgeons is required.

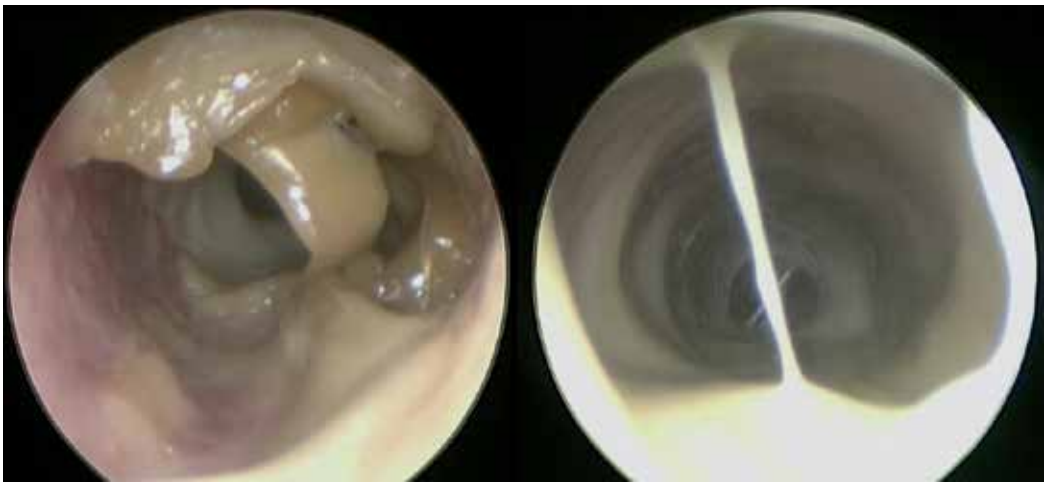

Figure 8. A 9-year-old patient presenting with cough and stridor with concurrent fever. Direct laryngoscopy with rigid bronchoscopy revealed bacterial tracheitis. Tracheal casts can cause airway symptoms similar to aspirated foreign bodies.

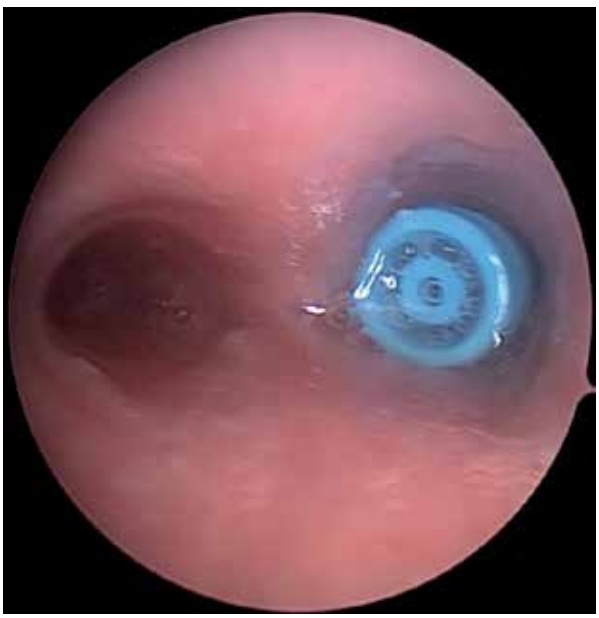

Figure 9. A 12-month old presented to the Emergency Department with increased work of breathing and stridor after reportedly having swallowed a piece of a pen. Plain film imaging was unrevealing. Given the clinical presentation, the patient underwent direct laryngoscopy with rigid bronchoscopy, revealing a plastic foreign body in the right mainstem bronchus.

http://dx.doi.org/10.5772/60590

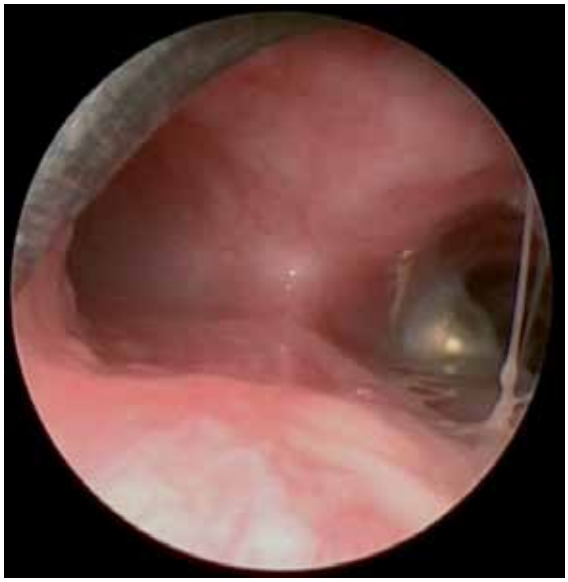

Figure 10. A 12-month old presenting with respiratory symptoms and concern for foreign body aspiration. Direct laryngoscopy with rigid bronchoscopy confirms a high-powered magnet sphere within the right mainstem bronchus. Another was trapped in the esophagus directly behind this. This has the potential to cause a tracheoesophageal fistula given magnetic strength and tissue necrosis between the two magnets. Severe injuries are more common in the lower gastrointestinal tract causing perforation when more than one of these is swallowed (this child had additional magnetic spheres in the small bowel which caused transmural necrosis and perforation requiring repair).

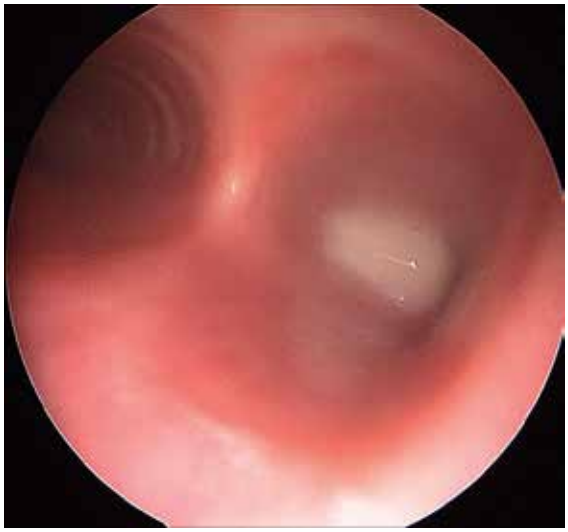

Figure 11. While having a tooth extracted at a dentist office, this child accidently aspirated the tooth, found in the right mainstem bronchus.

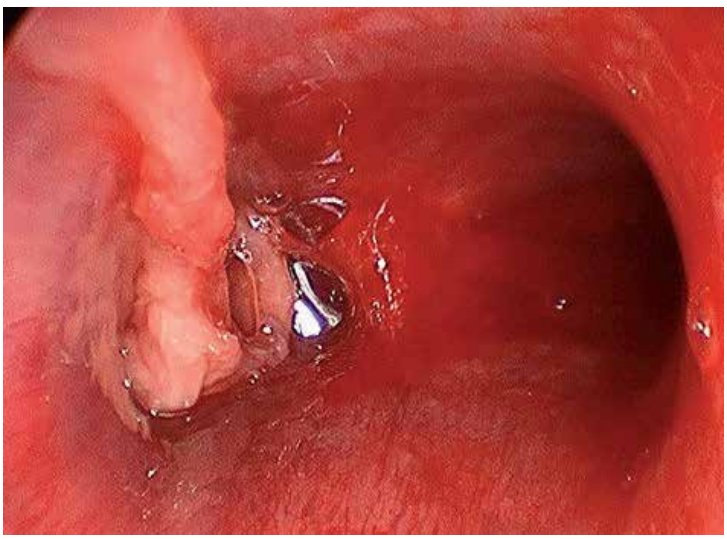

Figure 12. Plastic bronchitis in a patient with congenital heart disease, showing a cast in the left bronchial tree.

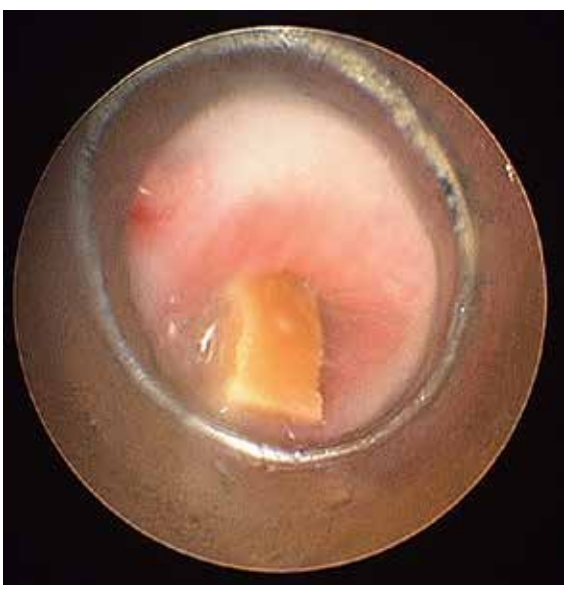

Figure 13. A 2-year-old boy was given peanuts by an older sibling, choked, was in severe respiratory distress, found to have several fragments in the lower airways. These were removed with optical graspers through the rigid bronchoscope.

http://dx.doi.org/10.5772/60590

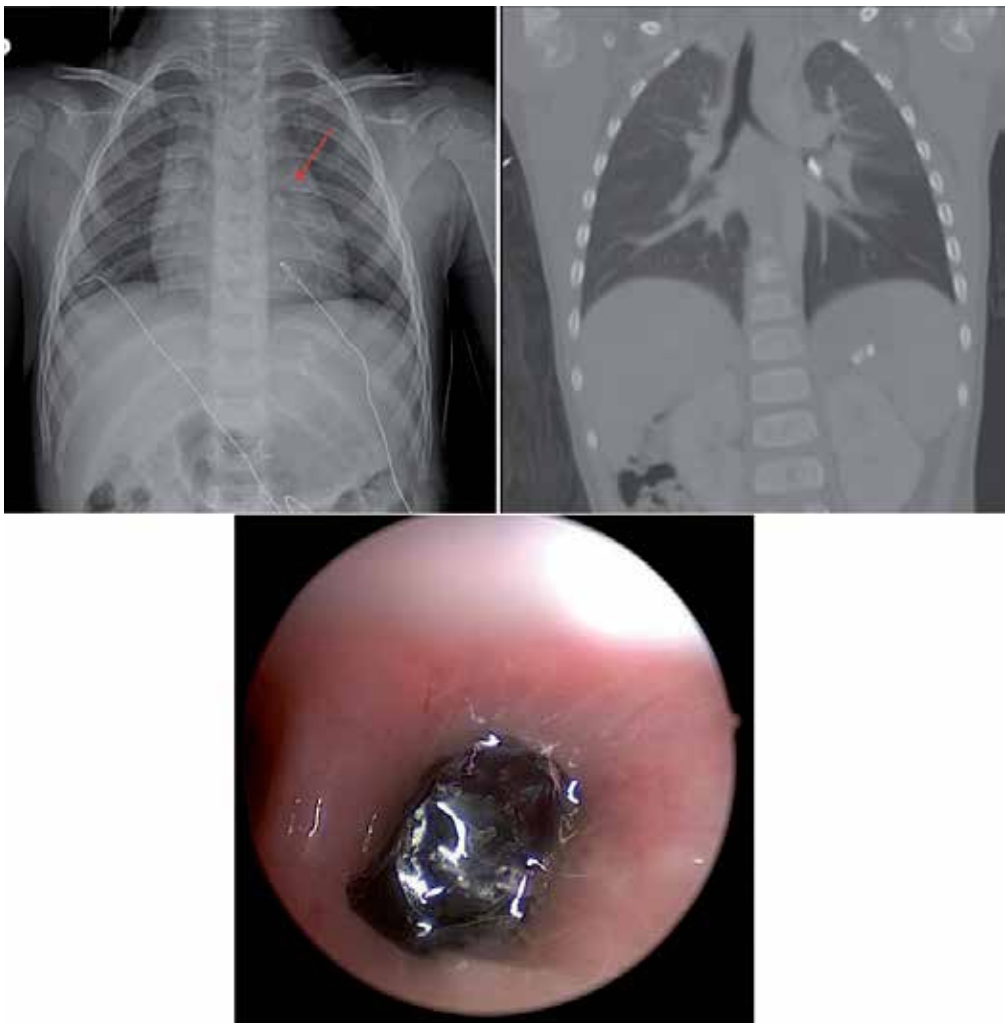

Figure 14. A 2-year-old patient presented to the Emergency Department with multiple facial lacerations following a motor vehicle accident during which she was ejected through the passenger side window. She had no respiratory symptoms as presentation. As part of her trauma workup, she underwent both plain film and CT imaging of the chest, both showed a possible left-sided airway foreign body. Direct laryngoscopy with bronchoscopy confirmed the diagnosis, and the object was endoscopically removed without difficulty.

6. Pediatric Esophageal Foreign Bodies

6.1. Epidemiology

Foreign body ingestion is a relatively common occurrence, with an estimated 100, 000 cases per year in the United States alone. Like airway foreign bodies, the majority of cases occur in children aged between 6 months and 3 years [33]. For the majority of esophageal foreign bodies,

a child's caregiver either witnesses or suspects that their child has ingested a foreign body [34]. While the majority of ingested foreign bodies will pass on their own, there is still a real risk of significant morbidity and mortality. Of all patients with esophageal foreign bodies seeking medical attention, 80%–90% pass the foreign body without any intervention, 10%--20% require endoscopic removal, and only 1% require surgical removal [33]. It has been estimated that 1, 500 deaths occur annually in the United States alone due to foreign body ingestion [35].

Recently, there has been a sharp rise in the use of button-battery powered hand-held electronic equipment. This has coincided with a rise in the incidence of button battery--related emergency department visits [36].

6.2. Clinical presentation

As with airway foreign bodies, a thorough history and physical exam are critical in the workup of the pediatric patient with a suspected esophageal foreign body. As previously stated, frequently, a caregiver has witnessed the ingestion and can positively identify the object, which may have implications regarding urgent intervention, such as in the case of an ingested button battery or magnet.

Many esophageal foreign body ingestions go unwitnessed and a large proportion of these pass without incident or development of symptoms [37]. When children do have symptoms, they tend to be nonspecific and can lead to a missed or delayed diagnosis. In a retrospective review by Arana et al. of 325 pediatric patients presenting with esophageal foreign bodies, only 54% of patients had transient symptoms at the time of ingestion [38]. When patients are symptomatic, they primarily present with nonspecific gastrointestinal or pulmonary complaints, including coughing, choking, gagging, drooling, odynophagia, and/or dysphagia. Patients may also present with stridor or wheezing due to inflammation of adjacent tracheobronchial mucosa.

In their retrospective study of 248 cases of patients undergoing esophagogastroduodenoscopy (EGD) for foreign body removal, Denney et al. assessed the incidence of esophageal injury as it related to presenting symptoms. In their series, 59 children (30%) were found to have mucosal ulceration. They found that a presenting complaint of substernal pain correlated with mucosal ulceration, whereas symptoms of vomiting, respiratory distress, and drooling did not. The vast majority of foreign bodies in their series were coins (81%) and 8 cases of batteries were reported. They did not comment on any injuries from batteries [34].

6.3. Radiographic evaluation

The patient's clinical presentation should be corroborated with imaging to ensure that a foreign body requiring urgent removal is not misdiagnosed [35]. Imaging for esophageal foreign body workup should typically include the chest and abdomen in both AP and lateral planes (Figure 15). It should be noted, however, that about 1/3 of foreign bodies are radiolucent [38].

Jatana et al. reported on the utility of plain film radiography in distinguishing esophageal coins from button batteries [39]. They described the "double ring" or "halo" sign created by a button

http://dx.doi.org/10.5772/60590

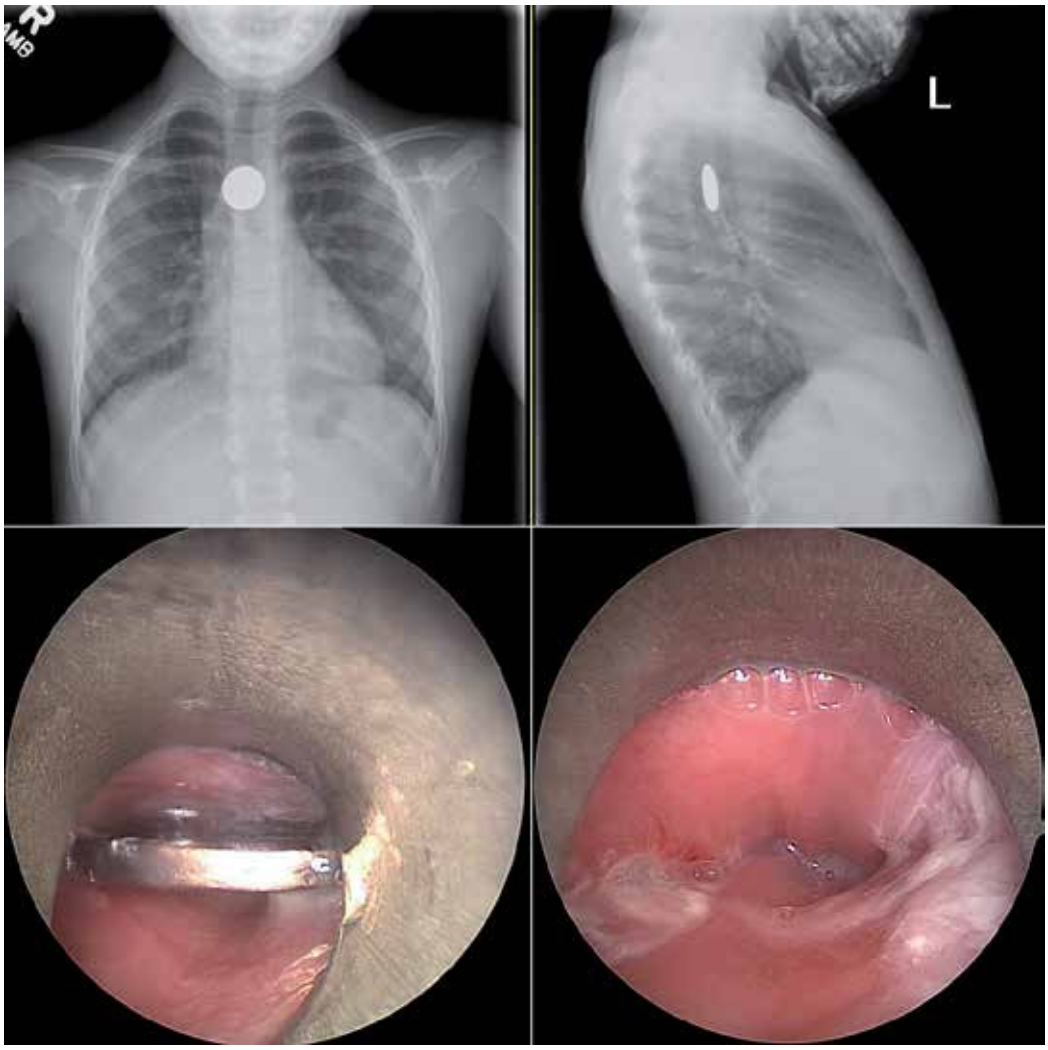

Figure 15. A 5-year old presented to the Emergency Department with several episodes of emesis. She admitted to swallowing a penny while at day care earlier that day. A-P and lateral plain films confirmed the diagnosis of an esophageal foreign body. A penny was identified and removed via rigid esophagoscopy. Minimal esophageal mucosal irritation was noted.

battery on an A-P plain film (Figure 16). The 20mm 3 volt lithium batteries consistently demonstrate this finding. They also demonstrated the "step-off" that can be seen on lateral plain films of button batteries, though they caution that some new thinner button batteries will not demonstrate this finding. Clinicians must not rely on lateral x-rays alone.

Many experts argue against the use of contrast studies for diagnosing esophageal foreign bodies given the increased risk of aspiration with a foreign body obstructing the esophagus. The presence of contrast could compromise the ability of the endoscopist to find the foreign body during retrieval and may also limit mucosal assessment [41]. In addition, the contrast

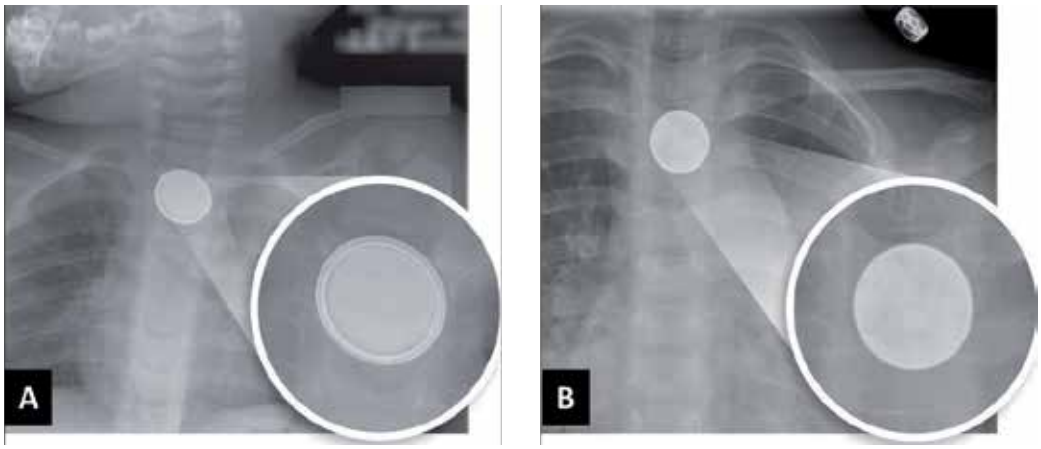

Figure 16. A) Button battery in upper esophagus. B) Coin in upper esophagus. By zooming into the foreign body, the "double ring or halo sign" can be clearly seen for the battery. Zooming into the image is most helpful for differentiation. Reproduced with permission, Jatana [40].

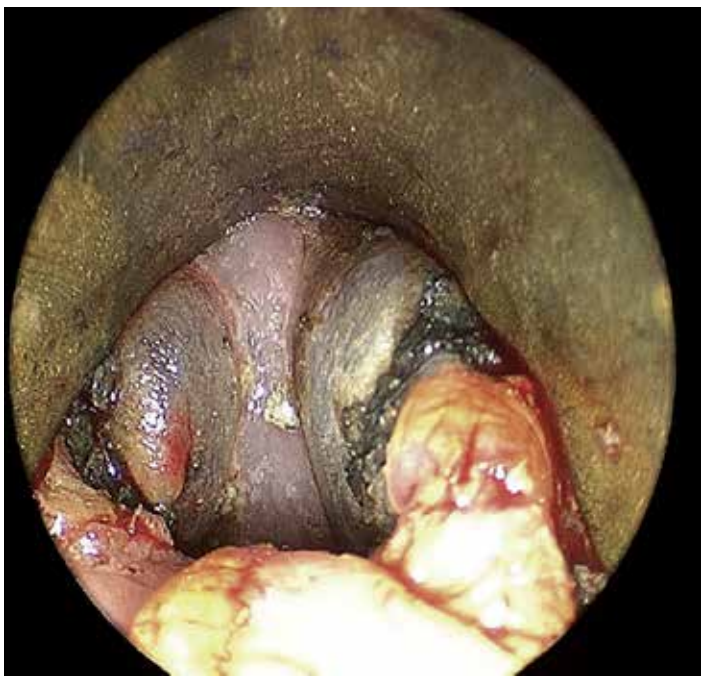

Figure 17. Esophageal injury secondary to a button battery in a 4-year old. The injury involves the muscular layer of the esophagus. Reproduced with permission, Jatana [40].

typically pushes back general anesthesia 8 h, and delays operative intervention. Esophagram does have a role in assessing for esophageal perforation or stricture due to foreign bodies, but generally only after operative removal of the foreign body.

Several authors have described the utility of hand-held metal detectors in the management of patients with suspected coin ingestion. Younger et al. performed a 2-year prospective study of patients presenting for evaluation of esophageal foreign bodies. With a hand-held metal detector, they were able to positively identify the presence and location of esophageal coins in all 26 patients who had positive plain films [42]. Lee et al. performed a systematic review of 11 studies and found that the sensitivity and specificity of identifying the presence of coins was 99.4% and 100%, respectively, when compared to plain films. They do note however, that non-coin metal objects were not detected as frequently as coins in one study reviewed. The authors point out the benefit of avoiding ionizing radiation when using a hand-held metal detector [43].

Repeat imaging has a role in the management of esophageal foreign bodies that are managed expectantly. An x-ray can ensure that an esophageal foreign body has passed into the stomach. In addition, should the object not be found in the stools over time, repeat abdominal x-ray can confirm that there is no retained opaque foreign body in the lower gastrointestinal tract.

6.4. Esophageal foreign body removal

Management of esophageal foreign bodies varies considerably based on several factors, including anatomic location, type of foreign body, patient presenting symptoms, and existing complications. A button battery lodged in the esophagus is an emergency. The current generated around the battery causes hydroxide ion to form at the negative pole, causing rapid injury. Serious injury can occur in only 2 h. The 20 mm diameter, 3 volt lithium batteries cause the most severe injury as they combine high power, with large enough size to get stuck; these are frequently used in many household electronics [39]. A common misconception is that the leaking battery acid is the major source of mucosal injury, rather than the generated electrical current. In addition, "dead" batteries, meaning those that no longer have enough charge to power their intended electronics, can still have enough residual electrical current to cause mucosal injury (Figure 17).

Coins lodged in the esophagus can be managed with an initial period of observation, and if they fail to pass into the stomach, can be removed endoscopically.

Rigid esophagoscopy allows for the scope to be placed under constant direct visualization for removal of the foreign body using endoscopic optical graspers that are most suited for the object. In general, a second-look esophagoscopy can not only confirm the absence of any additional non-opaque foreign bodies, but also assess any injury to the esophageal wall. If a perforation is suspected, keeping the patient with nothing by mouth and obtaining an esophagram is best. When probable perforation or known severe circumferential injury exists, consideration of placing a nasogastric tube under direct visualization through the rigid scope can serve as temporary means of nutrition and keep the region stented open to avoid complete stricture. It should also be kept in mind that when severe injury exists, advancing the esophagoscope past the site of injury can potentially lead to greater injury.

7. Complications of pediatric airway foreign bodies

The most feared acute complication of airway foreign bodies is complete airway obstruction with cardiopulmonary arrest and death. Wheezing is very common after the procedure and close monitoring in the hospital setting is required until symptoms have stabilized. Pneumonia is common due to lower airway obstruction and should be appropriately treated with antibiotics. Intraoperative cultures can be taken to help guide treatment. Given that injury can occur to the tracheobronchial tree, pneumomediastinum and pneumothorax can occur. When the airway is severely inflamed, bleeding and granulation tissue can limit visualization, and the decision to do a planned second-look bronchoscopy must be made to ensure no retained foreign body is present. Laryngeal injury when removing an airway foreign body can occur.

8. Complications of pediatric esophageal foreign bodies

Children who develop a fever after removal of any esophageal foreign body should be assessed for an esophageal perforation by esophagram. Other potential complications include: bleeding or major arterial fistula, mediastinitis, mediastinal abscess, respiratory distress (secondary tracheomalacia/compression), tracheoesophageal fistula, vocal cord paresis/paralysis, esophageal stricture, and death. Repeat endoscopy to follow healing of significant esophageal injury is an alternative to follow-up esophagram, and has the advantage of allowing for debridement or dilation of early stricture formation.

9. Conclusions

The management of pediatric airway and esophageal foreign bodies carries the potential for morbidity and mortality, and can be challenging to diagnose if an unwitnessed aspiration or ingestion occurs in a young child. The symptoms can be somewhat nonspecific, not easily differentiated from common viral illnesses in children. Clinical decision making based on thorough history and physical examination is critical. Centers with airway surgeons and endoscopists trained in foreign body management, and with pediatric ICU care are best equipped to manage the most complex cases in the children.

Author details

Phillip L. Chaffin, Jonathan M. Grischkan, Prashant S. Malhotra and Kris R. Jatana*

*Address all correspondence to: Kris.Jatana@nationwidechildrens.org

Department of Otolaryngology-Head and Neck Surgery, Nationwide Children's Hospital and Wexner Medical Center at Ohio State University, Columbus, Ohio, USA

References

[1] Gross SD, Samuel D. A practical treatise on foreign bodies in the air-passages (Internet). Philadelphia, Blanchard and Lea; 1854 (cited 2015 Jan 4). p. 498. Available from: http://archive.org/details/practicaltreagros

[2] Bush RB, Leonhardt H, Bush IM, Landes RR. Dr. Bozzini's Lichtleiter: A translation of his original article (1806). Urology. 1974 Jan;3(1):119–23.

[3] Desormeaux AJ, Antonin J, Hunt RP. The endoscope, and its application to the diagnosis and treatment of affections of the genito-urinary passages: lessons given at Necker Hospital (Internet). Chicago: Robert Fergus' Sons, printers; 1867 (cited 2015 Jan 4). Available from: http://archive.org/details/65910730R.nlm.nih.gov

[4] Moore I. Peroral Endoscopy: An historical survey from its origin to the present day. J Laryngol Otol. 1926 Jun;41(06):361–82.

[5] Marsh BR. Historic development of bronchoesophagology. Otolaryngol Head Neck Surg. 1996 Jun;114(6):689–716.

[6] Thorner MM. A Utoscopy of the larynx and of the trachea. J Am Med Assoc. 1896 Feb 8;XXVI(6):265–7.

[7] Zöllner F. Gustav Killian, father of bronchoscopy. Arch Otolaryngol Chic Ill 1960. 1965 Dec;82(6):656–9.

[8] Hartnick CJ, Hansen MC, Gallagher TQ, editors. Pediatric Airway Surgery (Internet). S. Karger AG; 2012 (cited 2015 Jan 4). Available from: https://www.karger.com/Book/Home/255642

[9] Jackson C. Bronchoscopy and esophagoscopy. WB Saunders; 1922.

[10] Kenna MA, Bluestone CD. Foreign Bodies in the Air and Food Passages. Pediatr Rev. 1988 Jul 1;10(1):25–31.

[11] Nonfatal choking-related episodes among children--United States, 2001. MMWR Morb Mortal Wkly Rep. 2002 Oct 25;51(42):945–8.

[12] Gregori D, Salerni L, Scarinzi C, Morra B, Berchialla P, Snidero S, et al. Foreign bodies in the upper airways causing complications and requiring hospitalization in children aged 0-14 years: results from the ESFBI study. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2008 Aug;265(8):971–8.

[13] Tan HKK, Brown K, McGill T, Kenna MA, Lund DP, Healy GB. Airway foreign bodies (FB): a 10-year review. Int J Pediatr Otorhinolaryngol. 2000 Dec 1;56(2):91–9.

[14] Shubha AM, Das K. Tracheobronchial foreign bodies in infants. Int J Pediatr Otorhinolaryngol. 2009 Oct;73(10):1385–9.

[15] Skoulakis CE, Doxas PG, Papadakis CE, Proimos E, Christodoulou P, Bizakis JG, et al. Bronchoscopy for foreign body removal in children. A review and analysis of 210 cases. Int J Pediatr Otorhinolaryngol. 2000 Jun 30;53(2):143–8.

[16] Chapin MM, Rochette LM, Annest JL, Haileyesus T, Conner KA, Smith GA. Nonfatal choking on food among children 14 years or younger in the United States, 2001-2009. Pediatrics. 2013 Aug;132(2):275–81.

[17] Trachea Foreign Bodies. 2013 Jul 9 (cited 2015 Jan 5); Available from: http://emedicine.medscape.com/article/764615-overview

[18] Chinski A, Foltran F, Gregori D, Ballali S, Passali D, Bellussi L. Foreign bodies in children: A comparison between Argentina and Europe. Int J Pediatr Otorhinolaryngol. 2012 May 14;76, Supplement 1:S76–9.

[19] Claudet I, Salanne S, Debuisson C, Maréchal C, Rekhroukh H, Grouteau E. Corps étranger nasal chez l'enfant. Arch Pédiatrie. 2009 Sep;16(9):1245–51.

[20] François M, Hamrioui R, Narcy P. Nasal foreign bodies in children. Eur Arch Otorhinolaryngol. 1998;255(3):132–4.

[21] Gregori D, Salerni L, Scarinzi C, Morra B, Berchialla P, Snidero S, et al. Foreign bodies in the nose causing complications and requiring hospitalization in children 0-14 age: results from the European survey of foreign bodies injuries study. Rhinology. 2008 Mar;46(1):28–33.

[22] Rodríguez H, Passali GC, Gregori D, Chinski A, Tiscornia C, Botto H, et al. Management of foreign bodies in the airway and oesophagus. Int J Pediatr Otorhinolaryngol. 2012 May 14;76, Supplement 1:S84–91.

[23] Assefa D, Amin N, Stringel G, Dozor AJ. Use of decubitus radiographs in the diagnosis of foreign body aspiration in young children. Pediatr Emerg Care. 2007 Mar;23(3): 154–7.

[24] Silva AB, Muntz HR, Clary R. Utility of conventional radiography in the diagnosis and management of pediatric airway foreign bodies. Ann Otol Rhinol Laryngol. 1998 Oct;107(10 Pt 1):834–8.

[25] Zerella JT, Dimler M, McGill LC, Pippus KJ. Foreign body aspiration in children: Value of radiography and complications of bronchoscopy. J Pediatr Surg. 1998 Nov; 33(11):1651–4.

[26] Brown JC, Chapman T, Klein EJ, Chisholm SL, Phillips GS, Osincup D, et al. The utility of adding expiratory or decubitus chest radiographs to the radiographic evaluation of suspected pediatric airway foreign bodies. Ann Emerg Med. 2013 Jan;61(1): 19–26.

[27] Kocaoglu M, Bulakbasi N, Soylu K, Demirbag S, Tayfun C, Somuncu I. Thin-section axial multidetector computed tomography and multiplanar reformatted imaging of

children with suspected foreign-body aspiration: Is virtual bronchoscopy overemphasized? Acta Radiol Stockh Swed 1987. 2006 Sep;47(7):746–51.

[28] Haliloglu M, Ciftci AO, Oto A, Gumus B, Tanyel FC, Senocak ME, et al. CT virtual bronchoscopy in the evaluation of children with suspected foreign body aspiration. Eur J Radiol. 2003 Nov;48(2):188–92.

[29] Zur KB, Litman RS. Pediatric airway foreign body retrieval: surgical and anesthetic perspectives. Paediatr Anaesth. 2009 Jul;19, Suppl 1:109–17.

[30] Fidkowski CW, Zheng H, Firth PG. The anesthetic considerations of tracheobronchial foreign bodies in children: a literature review of 12, 979 cases. Anesth Analg. 2010 Oct;111(4):1016–25.

[31] Park AH, Tunkel DE, Park E, Barnhart D, Liu E, Lee J, et al. Management of complicated airway foreign body aspiration using extracorporeal membrane oxygenation (ECMO). Int J Pediatr Otorhinolaryngol (Internet). 2014 Oct (cited 2015 Jan 7); Available from: http://linkinghub.elsevier.com/retrieve/pii/S016558761400576X

[32] Ulkü R, Onen A, Onat S, Ozçelik C. The value of open surgical approaches for aspirated pen caps. J Pediatr Surg. 2005 Nov;40(11):1780–3.

[33] Wyllie R. Foreign bodies in the gastrointestinal tract. Curr Opin Pediatr. 2006;18(5): 563–4.

[34] Denney W, Ahmad N, Dillard B, Nowicki MJ. Children will eat the strangest things: a 10-year retrospective analysis of foreign body and caustic ingestions from a single academic center. Pediatr Emerg Care. 2012;28(8):731–4.

[35] Uyemura MC. Foreign body ingestion in children. Am Fam Physician. 2005 Jul 15;72(2):287–91.

[36] Sharpe SJ, Rochette LM, Smith GA. Pediatric battery-related emergency department visits in the United States, 1990-2009. Pediatrics. 2012 Jun;129(6):1111–7.

[37] Dahshan A. Management of ingested foreign bodies in children. J Okla State Med Assoc. 2001 Jun;94(6):183–6.

[38] Arana A, Hauser B, Hachimi-Idrissi S, Vandenplas Y. Management of ingested foreign bodies in childhood and review of the literature. Eur J Pediatr. 2001;160(8):468–72.

[39] Jatana KR, Litovitz T, Reilly JS, Koltai PJ, Rider G, Jacobs IN. Pediatric button battery injuries: 2013 task force update. Int J Pediatr Otorhinolaryngol. 2013 Sep;77(9):1392–9.

[40] Jatana K. Button Battery Injuries in Children: A Growing Risk. Everything Matters in Patient Care. Nationwide Children's Hospital, Columbus, OH; 2013.

[41] Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Guideline for the management of ingested foreign bodies. Gastrointest Endosc. 2002 Jun;55(7):802–6.

[42] Younger RM, Darrow DH. Handheld metal detector confirmation of radiopaque foreign bodies in the esophagus. Arch Otolaryngol Neck Surg. 2001 Nov 1;127(11):1371–4.

[43] Lee J, Ahmad S, Gale C. Detection of coins ingested by children using a handheld metal detector: a systematic review. Emerg Med J EMJ. 2005 Dec;22(12):839–44.

Edited by Somchai Amornyotin

Endoscopy is a fast moving field, and new techniques are continuously emerging. In recent decades, endoscopy has evolved and branched out from a diagnostic modality to enhanced video and computer assisting imaging with impressive interventional capabilities. The modern endoscopy has seen advances not only in types of endoscopes available, but also in types of interventions amenable to the endoscopic approach. To date, there are a lot more developments that are being trialed. Modern endoscopic equipment provides physicians with the benefit of many technical advances. Endoscopy is an effective and safe procedure even in special populations including pediatric patients and renal transplant patients. It serves as the tool for diagnosis and therapeutic interventions of many organs including gastrointestinal tract, head and neck, urinary tract and others.

ISBN 978-953-51-7258-1

Photo by kot63 / iStock

IntechOpen